BRUCELLOSIS

(UNDULANT FEVER)

SECOND EDITION, REVISED AND ENLARGED

BRUCELLOSIS

(UNDULANT FEVER)

Clinical and Subclinical

by

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with the assistance of

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David Bruce

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FOREWORD

The most constant occurrence in life is constant change. In no field of human endeavor is this fact more evident than in medicine. The average medical practitioner is often overwhelmed by the avalanche of reports of newly discovered disease entities and of new therapeutic agencies. Too often such reports, based upon superficial observations, fade from medical consciousness when exposed to the white light of objective critical analysis.

It was quite natural, therefore, that the early reports of the apparently widespread dissemination of brucellosis were greeted with considerable skepticism. The successive reports of many reliable investigators during the past decade, however, permit of no doubt that brucellosis is an important public health problem, world-wide in its distribution and most prevalent among human beings in those areas in which *Brucella* infection of cattle, hogs and goats is widespread. It is pertinent to direct attention to the fact that the several competent investigators who set out deliberately to determine the incidence of the disease among local raw milk consuming populations have succeeded invariably in establishing the common occurrence of brucellosis in such circumscribed areas. The inference is obvious that the disease is much more prevalent than the official reports of state Health Departments would indicate.

American physicians have gradually become aware of the wide prevalence of the acute form of brucellosis. Their alertness has been rewarded by their discovery that many patients suffering from unconfirmed typhoid-like, malaria-like or tuberculosis-like disease were actually victims of brucellosis.

More recently there has accumulated unmistakable evidence that chronic brucellosis is even more common than the acute

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ment of present-day knowledge of brucellosis. This monograph will undoubtedly achieve the purpose for which it was prepared, namely, to help the great mass of people suffering from brucellosis by making their physicians brucellosis-minded.

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form of the disease and that it constitutes a major cause of chronic ill health. While many physicians now feel that the symptoms and signs of acute brucellosis are sufficiently characteristic often to justify such a provisional diagnosis on the basis of clinical findings, chronic brucellosis presents problems which will frequently tax the diagnostic acumen of the physician to the utmost. The relative value of the diagnostic tests, other than isolation and identification of the causal organism, is a subject for disagreement even among investigators of the disease. No test, excepting successful culture of *Brucella*, has been devised which supplants clinical skill and judgment. The urgent need for simpler and more certain diagnostic aids is apparent.

Doctor Harold J. Harris is deserving of high praise for the preparation of this needed monograph. Originally an active practitioner of medicine in a rural area, faced with the necessity of overcoming a lack of adequate local facilities for laboratory studies, he was stimulated to pursue the studies which provide the background for this monograph by the growing conviction that he had often failed to recognize brucellosis during the early years of his practice. In the first edition, published in 1941, Doctor Harris consequently placed particular emphasis upon the clinical aspects of brucellosis, based upon close personal observations made upon some 250 patients with the disease. That treatise was addressed chiefly to the general practitioner, to whom the opportunity is usually first presented for the recognition of brucellosis

The revision of this book has been complete in every chapter. Observations on an additional 450 patients have been included A new chapter on psychologic studies has been added Annotation of bibliography and appropriate subheading of the large mass of material included should make this volume a text and reference source for the general practitioner and for the specialist in every field of medicine

It has been aptly stated that "the first consideration in the diagnosis of brucellosis is to think of brucellosis" Doctor Harris has prepared a clear, concise, convincing and authoritative state-

PREFACE TO THE SECOND EDITION

THE first edition of this monograph was based on observations made on some 250 cases of brucellosis between 1932 and the date of publication in 1941. With minor exceptions, the ideas and findings originally set forth still obtain. The main purpose of revision is to elaborate more fully on some phases of this intricate subject and to introduce new observations made by the author and others. For example, further evidence of the importance of *Brucella* infection in the etiology of an important but unknown percentage of arthritis has come to light. The incidence of salpingitis in brucellosis has been further demonstrated. The numerous ocular manifestations of brucellosis have been observed to a much greater extent during that period (or perhaps it would be more accurate to say that fewer errors in the diagnosis of ocular involvement have been made). Greater stress has been placed on laboratory aids and their proper interpretation. Treatment methods have been brought up-to-date.

Work on the psychosomatic aspects of chronic brucellosis was initiated during the war and has been expanded since, with the aid of expert clinical psychologists. It has been of inestimable value to have psychologic studies, including the Rorschach method, of all patients in whom there was a preexisting psychologic state or in whom such states were precipitated or aggravated by chronic illness In many instances the distinction between clinical brucellosis and clinical degrees of psychoneurosis was greatly facilitated by these studies In others their relative importance and possible inter-relationship, when they co-existed, was elucidated

The new material has been gleaned from the study of about 450 additional patients, including Navy personnel and their de-

nostic problems. Although much is still to be desired in this direction, the progress made is gratifying.

It was over fifty years ago that Hughes, in his monograph, *Mediterranean, Malta or Undulant Fever,* said: "There is a great tendency on the part of some medical men to believe that the disease must have recently appeared, because they themselves previously failed to recognize it." Apparently the tendency was as great in 1897 as it is today for authors to grouse about the failure of recognition of their chosen fields of study. Actually, the observation applied a great deal more in the years in which Hughes worked and wrote than it does in this immediate postwar period The disease *is* being accorded the importance which is its due by larger and larger percentages of physicians throughout the world

Overenthusiasm is bound to occur, as it has and will in other fields of medicine. Because brucellosis can closely simulate so many diseases, including the psychoneuroses, it is bound to be suspected or even firmly diagnosed by some, in the absence of sufficient study There is a tendency, perhaps because of the intricacy and time-consuming nature of the differential studies necessary, to perform skin tests alone and to diagnose brucellosis whenever such tests are positive It is to be hoped that, as diagnostic methods are improved, such an inaccurate means of diagnosis will be discarded

The concept that there is a chronic illness occurring in large numbers of patients with only low-grade or no actual febrile response has been exceedingly slow in acceptance, in spite of adequate evidence of its frequent occurrence It is unfortunate but not surprising that, when acceptance of chronic brucellosis as a clinical entity was achieved, the diagnosis has been seized upon as an explanation for many obscure illnesses without adequate evidence of its accuracy. (The term "evidence" instead of "proof" is purposefully chosen for, even under the most careful study, proof through culture often is lacking but clinical and laboratory evidence on a strongly presumptive basis is present.)

It seems properly within the scope of this book to review some

pendents and civilians since 1941, and from the current literature (which still contains much that is controversial). Many of the patients studied prior to the war have again come under observation. The conclusions drawn are therefore based on the observations and treatment of about 700 patients, some of whom have been followed for fifteen years.

The number of cases of brucellosis among Navy personnel unquestionably would have been much larger had the author's service been confined to the medical wards of naval hospitals. During six months of such hospital service as medical officer in charge of wards of acute infectious diseases, 14 cases of previously unsuspected brucellosis were diagnosed. As senior medical officer of a Navy receiving barracks, or serving in the same capacity on a combat troopship, little or no opportunity existed for the necessary observations of personnel who may have had clinical or subclinical brucellosis. However during the last two years of the war, while assigned to psychiatric work ashore, 12 additional instances of active brucellosis were encountered incidentally during psychiatric observation or through reference by other medical officers via official channels At no time was brucellosis the object of a special naval research project. Therefore, the cases encountered were, except in a few instances, diagnosed or diagnosable only because of "brucellosis-mindedness." The laboratory work necessary was not usually available in naval hospitals or dispensary laboratories With the approval of the Bureau of Medicine and Surgery, U S Navy, the special laboratory procedures were carried out privately whenever on shore duty It is obvious that only a small fraction of the number of actual cases encountered, casually or otherwise, could have been diagnosed The sick-bay of a ship or of a shore establishment, in time of war, does not lend itself to that meticulous study of patients which is so essential if brucellosis, especially in its chronic phase, is to be diagnosed or ruled out

It can now be said that a growing percentage of physicians, in general practice and in the specialties, are coming to realize that brucellosis must be included regularly in their differential diag-

than the brief periods of observation afforded by patients on hospital wards. The opportunity to follow patients for long periods has allowed correction of diagnostic errors as well as better evaluation of treatment methods. Valuable though hospital observation is under some circumstances, much of its importance is destroyed by necessary haste or by failure to correlate findings with those made before and following such study.

Infection in animals is discussed only from the standpoint of its relation to human disease.

The diagnosis and treatment of brucellosis have become as proper a specialty as is syphilology or phthisiology. It is deserving of devotion of full time to its study and of greater attention in the curricula of schools of medicine.

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of the experimental and clinical evidence on which conclusions of various work have been based, even at the risk of seeming contentious. The obvious purpose of this detailed exhibition is to attempt to sort the wheat from the chaff and to present conclusions based on clinical and laboratory evidence which will stand careful scrutiny and will be of practical value to the physician. The wisdom of such a policy may be open to question. It has been followed on the theory that failure to disagree with viewpoints expressed in current literature or reference books implies agreement.

Unfortunately the methods to be used in the diagnosis of brucellosis are still the subject of controversy. All procedures which can throw any light on the problem should be employed, always bearing in mind the limitations of each procedure. Dependence upon the agglutination reaction and culture alone will inevitably result in failure to diagnose an important percentage of cases of obscure brucellosis The opsonocytophagic and complement fixation reactions should be looked upon as adjuvant tests. The intradermal reaction may not be omitted unless other evidence is sufficient to indicate the existence of brucellosis. As corroboratory evidence, the trial of specific treatment needs no justification, if carefully employed and interpreted.

An attempt has been made to digest the useful information from the entire literature. This has led to unavoidable repetition. The excuse is too often made, even now, that "brucellosis really is a rare disease," or "that it is dying out as a result of the almost universal pasteurization of milk," as was said by the editor of one of the [illegible] firms recently, or that "it is a [illegible]" or that "there is no treatmen[illegible] To include the entire literature would result in confusion and unnecessary wordiness for many reports are based on assumption alone or upon inadequate observation

Perhaps the author's greatest advantage in the study of chronic brucellosis lay in the opportunity for prolonged observation of private patients among fairly stable population groups rather

cies are the persistently recurring ideas that the dise[illegible]
common, that it is self-limited, that it [illegible]
the finding of a high [illegible]
tion test rules out [illegible] by such
procedures as intr[illegible]ccine, neoarsphenamine or
by time alone.

It is hoped that, among other lessons, it will be shown that brucellosis is a problem that has been with us for many years past, that it will be for years to come, and that it is worthy of all our efforts, along preventive as well as therapeutic lines.

Until recently, and perhaps in some schools still, medical students were taught to think of brucellosis as a rare disease to be suspected only if the patient exhibited a long-continued fever, resembling typhoid, but in which laboratory findings were negative for typhoid Two patients, both young farmhands, who presented themselves for diagnosis of chronic ailments in 1932, proved the fallacy of this conception. Both became acutely ill with high fever, while under observation, one because of frequent nosebleeds and the other because of a peptic ulcer syndrome Both ran a prolonged typhoid-like fever and then recovered, after stormy courses, to about the same status as before the acute illness Both had high blood agglutination titers with *Brucella abortus* (during the acute exacerbations) The symptoms in one case had been recurrent for nine years before the acute illness and in the other for four years It seemed logical to suspect that these patients had actually been suffering from the chronic phase of an illness for nine and four years, respectively, and that the acute illness had been a phase in the infection, followed by another chronic phase It was natural then to wonder if there were not many other instances of just chronic brucellosis which had been wrongly diagnosed . . . Confirmation was not slow in coming.

Close contact with and personal knowledge of patients proved of inestimable help in the evaluation of methods of treatment. Many ineffective methods were tried and discarded It was possible to do what the staff of a well-organized hospital finds ex-

In its own chapter, diagnosis is discussed in detail from the following standpoints:

A. Clinical history and findings.
B. Laboratory criteria
    1. Definitive: Culture of the organism—a final and unquestioned method if positive.
    2. Probable: Blood agglutination test, skin test, opsonocytophagic test, which tend to be confirmatory of clinical diagnosis, when positive; their individual and relative importance are discussed in detail.
C. Response to therapeutic test of specific vaccine. This means of arriving at a conclusion in doubtful cases has proved of inestimable value but its results are subject to gross misinterpretation unless coincidence, psychologic response, and nonspecific effects are constantly evaluated.

To use therapeutic response as one link in a chain of evidence needs explanation but no defense. To avoid its use in brucellosis, for which all of the four existing tests are notoriously inadequate if negative, is to invite erroneous diagnosis in a great many actual cases The method cannot be recommended to anyone who is unwilling to approach the individual problem with an entirely open mind or to revise his tentative diagnosis if evidence warrants. The patient becomes an active partner in the therapeutic test in these instances, and therefore must be exceptionally cooperative.

Symptomatology, diagnosis, and treatment are discussed together in many parts of the monograph because they are often so inextricably involved with each other Some repetition is therefore unavoidable.

An attempt is made throughout this work to refute some widely accepted ideas which have been proved erroneous, through personal observations and observations of others Many misconceptions as to diagnosis and treatment are still adopted by one author after another, on the basis of errors of twenty or more years ago, and appear in texts and in current literature. Among these falla-

things that almost all important physiological discoveries that are immediately applicable to the treatment of disease have their original source in clinical observation"—Sir Thomas Lewis: Research in Medicine and Other Addresses, London, H. K. Lewis & Co., Ltd., 1939.

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tremely difficult—to know clinically as well as through repeated laboratory study how patients were at the end of a year or five years following the conclusion of treatment.

Because a patient, whose symptoms [and laboratory studies] suggest brucellosis makes an apparently excellent clinical response to [*Brucella*] vaccine therapy, it must not be assumed that his report of subjective improvement is absolute evidence that he was suffering from brucellosis or that he is recovering due to specific treatment. The attending physician must maintain a degree of skepticism even in the face of the very evidence he seeks, *if he is to avoid avoidable errors and chagrin. He should* seek to have the favorable clinical evidence amply confirmed by prolonged observation of the patient and by laboratory criteria of recovery. He must always remember that coincidence can simulate effect and that psychotherapy may have been used unwittingly along with other therapy. If this degree of openmindedness is maintained, if there is adequate proof of diagnosis (clinical and laboratory) and if there is also clinical and laboratory evidence of recovery, little is left to chance The possibility of nonspecific protein effect is discussed more fully in the chapter on treatment.

Several conditions are mentioned as possibly or probably due to brucellosis that have not had adequate confirmation nor disproof. Some are discussed for obvious reasons, for they have occurred too often to be ignored. Others are mentioned largely to provoke and promote discussion and study at the hands of those who are equipped to do it Nothing is definitely ascribed to brucellosis unless culture in that case or in similar cases has been positive.

"Knowledge that is to be applied usefully to the health of mankind will almost always come by a series of steps, the first of which is the recognition of the human need, the last of which is the application of a test directly to the human problem It is in the nature of things, however many steps may intervene, that the first and last must be clinical, as it is also in the nature of

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ACKNOWLEDGMENT is here made to the Macmillan Company for the wealth of material gleaned from Hughes' monograph *Mediterranean, Malta or Undulant Fever*, published in 1897; to Harrison and Son, publishers of the epoch-making *Reports of the Commission Appointed by the Admiralty, the War Office, and the Civil Government of Malta, for the Investigation of Mediterranean Fever, under the Supervision of an Advisory Committee of the Royal Society* (1905 to 1907); to Edward Arnold and Company, London (William Wood and Company, Baltimore) for details of bacteriology from *The Principles of Bacteriology and Immunity*, by Topley and Wilson, published in 1936, to Williams and Wilkins, publishers of Wadsworth's *Standard Laboratory Method* (1947); as well as to other authors and publishers not specifically named To the Division of Laboratories and Research of the New York State Department of Health acknowledgment is made for the vast numbers of laboratory procedures carried out and for the cooperation of the staff, notably that of Dr Ruth Gilbert. To Jacoba V. Schochat, B A, appreciation is extended for technical assistance I am indebted to Dr. Lee Foshay for the exchange of ideas and criticism of theories and practice. Appreciation also is extended to Dr. Ruth Munroe, Dr Molly Harrower, and Miss Camilla Kemple for the help afforded by their expert psychologic studies To Dr. Walter Simpson, one of the foremost early workers in the field of brucellosis, appreciation is extended for invaluable suggestions and advice in the preparation of the manuscript for both editions. To the Committee on Scientific Research of the American Medical Association and to the Lilly Research Laboratories acknowledgment is made for grants-in-aid of some aspects of the clinical and laboratory research incorporated in the second edition

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BRUCELLOSIS

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Chapter I

INTRODUCTION

Historical

THE ecology of *Brucella* has been inadequately studied Much has to be pure speculation Eyre stated his belief that *Brucella* infection of the goat had its origin in the Persian hills, Nicolle thought that the infection followed the migrations of the English race and the exportation of Maltese goats Huddleson, however, has pointed to evidence that brucellosis in goats and man was experienced in Spain and adjoining countries in the early fifteenth century, before the English had entered the Mediterranean to any extent He thought that the disease was then brought from Spain to the Americas by the Spanish invaders Which of the strains was the first and the order in which they became adapted to their hosts has not been proved.

Hughes[363] stated that the accurate history of brucellosis began with Marston in 1859, although the disease must have existed along the Mediterranean for more than one hundred years before that date He and others have pointed out that significant references in the *Epidemica* of Hippocrates suggested that this disease dates back as far as 450 B C Other historical references to the disease, of unknown accuracy, were attributed by Hughes to Demarco, Cleghorn, Howard, Fauverge, Burnet, Hennen, Heastie, Davy, and others, between 1722 and 1835

The earliest known reference to brucellosis, between the time of Hippocrates and of Marston, was that of Moscall in 1567, who referred to the infectiousness of abortion in cattle. Other refer-

ent undefined forms of fever which to a certain extent resemble this undulant fever."

Hughes compiled statistics showing the admission rate of "simple continued and remittent fevers" for the years 1817 through 1889. These varied from 176.3 during the twenty years from 1817 to 1836, to 128.5 during the years 1880 through 1889. The highest rate was 256 per thousand between 1847 and 1856 Mortality varied from .93 to .308.

During the Crimean War, when Malta was an important military base, this disease first attracted great attention and was for the first time intensively studied by Marston. Mackay in 1892 and Pottinger in the same year made significant observations regarding some of their "typhoid" cases, which leave little doubt that they were referring to undulant fever; they recognized that their cases were atypical, and called attention to various complications now recognized as manifestations of this disease. Boilleau and Chartres, writing in the Army Medical Blue-Books between 1865 and 1866, described under the name "Mediterranean gastric remittent fever" cases which are now believed, on the basis of clinical and postmortem details, to have been undulant fever In the meantime, civil practitioners in England had written of atypical typhoid or of atypical typho-malarial fevers in patients who were being invalided home from the Mediterranean.

Surgeon J. S Chartres [137] reported extensively on "Mediterranean gastric remittent fever as an endemic in the 100th Regiment in 1866"

In 1876 Franck inoculated healthy pregnant cows with infective material from aborting animals, producing abortion

In discussing possible modes of propagation and dissemination, Hughes (1897) said:

> That the disease is not propagated by direct contagion from man to man is the fact that is agreed to by all observers . . It is difficult to say, in the present limited state of our knowledge, what is the exact mode by which the virus enters the human body

ences to the same subject were made in *The Complete Farmer* in 1807 and by British veterinarians in 1810. Bang[35] quoted *The Complete Farmer* as follows: "It is considered certainly contagious and when it happens the carcass should be immediately burned and the cows kept as widely apart as possible from the herd, and not receive the bull that goes with them."

From 1859, when Marston published his observations, until the time of Hughes, the outstanding contributions were made by Mackay in 1862, by Pottinger in 1862, by Boileau in 1865, by Chartres in 1866, by Guilia in 1871, by Donaldson, Wood and Notter in 1876, by Veale in 1879, by Turner in 1884, by MacLean in 1885, by Bruce in 1886, and by Moffet in 1889 The clinical descriptions given by these various writers were of inestimable value in leading subsequent observers to more accurate recognition of the disease as an entity. Hughes' monograph *Mediterranean, Malta or Undulant Fever*, published by Macmillan, London, in 1897, gave an historical and clinical study of brucellosis prior to the study of its epidemiology, which awaited the completion of the work of the Mediterranean Fever Commission nearly a decade later.

Many of these workers, including Marston and Hughes, suffered from the disease themselves and therefore were able to give first-hand accounts of its symptomatology. Practically all of the accounts were of long-continued fever, although Hughes recognized the possibility that pyrexias of short duration may also have been due to mild *Brucella* infections

Hughes stated that the disease was known to exist in Malta, Gibraltar, Sardinia, Balearic Islands, Italy, Sicily, Greece, Turkey, Cypress, Crete, Jerusalem, North Africa, in the Red Sea region, France, and India He expressed his suspicion of the prevalence of the disease in America from the reports of "typhomalarial fever" by Woodward in 1876, Maurel in 1879, Bartlet in 1881, and Webb in 1883 He recalled reports by Maury in 1881 of "malarial continued fever" in the Mississippi Valley. He drew the attention of his American colleagues to these "at pres-

superiority of milk pasteurized at a comparatively low temperature over boiled milk, Hughes recommended the use of a simple form of milk sterilizer which could be purchased or made locally.

During the American Civil War, Woodward[725] noted illnesses among soldiers which seemed to combine the symptoms of typhoid fever and malaria. Hoyt had described the same illness in 1873, as did Caulkins in 1878. In 1880 Hoff described four cases of typho-malarial fever and there was a succession of articles by various authors, including Fly in 1880 and Good in 1881. Caulkins was particularly impressed by the triad of high temperature, slow pulse, and excessive perspiration.

Discovery of the organisms by Bruce[87–91, 93] in 1886 grew out of his postmortem study of a patient who died on the fifteenth day of illness. He erroneously considered the organism to be a coccus rather than a bacillus, designating it *Micrococcus melitensis*. "Enormous numbers of single micrococci" were found in the splenic sections. In 1887 he unsuccessfully attempted culture of blood obtained by puncture of the finger tips. At autopsy in another case in 1887 he again recovered a similar organism. In a third case, he obtained splenic pulp after death, from which the same type of microorganism was recovered. The fourth case also yielded a "micrococcus." Altogether he recovered the organism from nine cases at autopsy. He reproduced the disease in monkeys by inoculating them with blood from the spleen of living patients.

In 1891 Bruce cultivated the same organism from blood aspirated from the spleen during life In only one autopsy did Bruce fail to recover the characteristic microorganism, apparently due to too alkaline a medium Between 1891 and 1897, the date of publication of his monograph, Hughes recovered the organism from the spleen of each one of 14 fatal cases of undulant fever, in no case was the microorganism absent.

Probably the next great milestone was the observation of Wright and Smith[731] (1897) that the blood agglutination reaction could be used to differentiate typhoid fever and Malta fever.

In the same year Wright and Semple[729] reported on the em-

He discussed water, beer, tea, and wines, absolving them all. Of milk, he said:

> The question of milk supply is intimately connected with that of water, most infection carried by milk being communicated by means of contaminated water fraudulently or purposely added, or used for cleaning vessels, etcetera. Besides this, the author has known undulant fever to attack families who used only Swiss condensed milk, regiments in which no other milk was allowed in Barracks, and families whose milk supply was always milk from goats milked on their own premises, into their own vessels, under reliable supervision He has met with no fact that would favor causal connection between milk supply and this fever. . . . Moreover, a large number of officers, ladies, women, children and even soldiers are attacked who never entered a grog shop, so that any cause derived from these places can scarcely be of peculiar nature, but common to other more respectable places.

By the process of exclusion Hughes concluded that polluted air was the most likely cause of this fever. In furtherance of his theory that the disease was spread through contaminated air from infected human feces, Hughes stated: "That the writer does not attach any fever-producing power to smells, per se, goes without saying, for indeed in such cases few dwellers in the Mediterranean would escape, but at the same time a smell is often an indication of sewer gas escape, and of the direction in which it travels."

Having absolved milk as a source of *Brucella* infection, Hughes quite naturally was led to the prescription of milk in the treatment of these sick patients. He remarked.

> In the countries where this fever occurs, goat's milk is always obtainable . . As goats can generally be brought to the patient's house, or to the hospital, and there milked under supervision, their milk is to be preferred to the more doubtful cow's milk, which is only obtained from the distance . Goat's milk thus obtained, in clean and well scalded vessels is excellent in quality and admirable for the purpose.

Because of the length of duration of the fever and the necessity of having the milk free from fermentation, and the great digestive

In Part I of the *Reports of the Commission*,[564] observations on the life of *Micrococcus melitensis* outside of the body, isolation of the organism from urine and feces, and methods of transmission and of cultivation were described.

In Part II [565] appeared epidemiologic data and observations on the virulence of the organism in the guinea pig.

Part III [566] dealt with cultural work on blood, sputum, urine, infectivity of skin, breath, and sweat, more on survival of the organism in various environments, examination of blood of infected goats, and goats as a means of propagation. Horrocks, in a separate report,[443] described Zammit's work which led to the first realization that goats were infected with Mediterranean fever.

In Part IV [567] data on the survival of the organism in earth and water, on goats as a source of propagation of the disease, on human ambulatory cases, and on the mosquito as a possible vector were presented.

In Part V [568] experiments on modes of infection and attempts to immunize monkeys, additional data on animal and human ambulatory infections, antiserum, and the bibliography relating to the disease were discussed.

In Part VI,[569] bacteriologic investigations involving the goat and the mosquito as vectors, infection in various animals, infection by personal contact, prophylactic vaccination, clinical observations, and various recommendations concerning prevention were discussed.

Recommendations made included compulsory notification, education as to sanitary measures, prohibition of export or import of animals subject to infection, education with regard to boiling goat's milk, prohibition of the use of fresh milk, use of preserved and condensed milk, registration of milk-giving animals, establishment of laboratories for detection of infected milk, slaughter of infected animals, segregation of healthy offspring and experimental use of *M. melitensis* vaccine.

There appeared in these reports an account ("Résumé of the Outbreak of Mediterranean Fever on Board the S.S. *Joshua*

ployment of dead bacteria in the serum diagnosis of typhoid and Malta fever. The same two authors published a report on the technic of serum diagnosis of "acute specific fevers."[730]

The year 1897 was a most productive one. In addition to the publication of Hughes'[369] monograph and the articles by Wright and Semple and by Wright and Smith, Bang[36] announced the isolation of a small bacillary organism from the pregnant uterus of a cow slaughtered for study because it presented symptoms of imminent abortion; he named the organism "*Bacillus abortus*." He considered it to be the etiologic agent of contagious abortion of cattle, which later was confirmed by various others.[453, 470, 515, 543]

In 1896 DaCosta,[154] describing long-continued fevers which he considered to be neither typhoid fever nor malaria, and which he suspected were "a type of their own," gave clear descriptions of brucellosis.

The first human case of "Malta fever" in the United States was reported in 1898 by Musser and Sailer.[505]

Craig[147] reported cases of brucellosis in the United States Army in 1904, including that of a nurse who had never been outside of the United States. He suggested that illnesses diagnosed as atypical typhoid fever were, in reality, undulant fever.

Second only in importance to the discovery of the organism by Bruce was the work of the Mediterranean Fever Commission, composed of Colonel Sir David Bruce, Fleet Surgeon T. W. Bassett-Smith, Major W. H Horrocks, Staff Surgeon E. A. Shaw, J. W. H. Eyre, Captain J Crawford Kennedy, Dr. T. Zammit, Dr. Ralph W. Johnstone, and others. The Commission had its origin in a letter from Mister Secretary Lyttelton, dated January 25, 1904, to the Royal Society, in which he stated that his attention had recently been called to the prevalence of Mediterranean fever in Malta among the naval and military forces as well as in the civil population

Embodied in these reports were many excellent studies which form the basis for an important part of the knowledge of brucellosis possessed today.

patients was reported. In a third report, Gentry and Ferenbaugh[252] confirmed the endemicity of *Brucella* infection in Texas and pointed out the probability that the large proportion of the cases diagnosed as atypical typhoid fever actually were *M. melitensis* infections. In a fourth contribution,[253] also in 1911, they reported that about 20 per cent of all goats examined had given a positive agglutination reaction with *M. melitensis*. All their human patients gave the history of association with goat raising and 6 gave a history of drinking goat's milk. Many of the goats were known to be direct descendants of goats imported from Asia Minor and South Africa where the disease had been proved to exist They also stated their belief that dust was a factor in human infection.

Yount and Looney[532] reported infection in goats in Arizona in 1913

The importance of the work of Larson and Sedgwick[426] in 1913 was not generally recognized They attempted to show the infectiousness of *Brucella abortus* for human beings and the value of the complement-fixation reaction in its detection.

Bacillus suis was isolated from the fetus of a sow by Traum[672] in 1914 and recognized as the cause of swine abortion.

Nicolle and Pratt,[512] in 1915, published observations which tended to confirm the opinion of Larson and Sedgwick as to the infectiousness of the *abortus* strain for man.

Good and Smith,[265] in 1916 confirmed the findings of Traum.

Certified raw milk was reported by Fleischner and Meyer[222] to yield *Brucella* organisms in 1917. It was not until 1930 that adequate efforts to produce certified milk, free of *Brucella*, were initiated

DeForest,[166] in 1917, published a truly prophetic report on the probable relationship between contagious abortion in cattle and abortion in women He had noted the coincidental illness and abortion in farm wives and among cattle, which bore such close similarity to each other as to leave no doubt in his mind that they were the same disease Attempts to prove the relationship bacteriologically failed

Nicholson") which undoubtedly is the accurate version of the importation of infected goats into America in 1905. It is reliably reported that, while these goats were en route from Malta to America, the British Commission for the Investigation of Mediterranean Fever, having established the fact that Maltese goats were vectors for *Brucella melitensis,* informed the U. S. Secretary of Agriculture of the danger. Tests by Mohler and Hart on the urine and milk and blood of the imported goats revealed the fact that several animals were infected. Efforts to eliminate the disease from the herds were unsuccessful and eventually all were destroyed.

It is apparent from these facts that these animals were not the source of *Brucella melitensis* infection among goats in the United States.

Following the prohibition of the use of raw goat's milk by men in the Army and Navy on Malta, issued on June 1, 1906, the incidence of brucellosis fell spectacularly. The average incidence for the years 1899 to 1905 had been from about 49 to 126; in 1906 the highest incidence was about 72, in 1907 about 4; in 1908 about 3, in 1909 about 2; and in 1910 about 2.

Determination of the phagocytic power of the white blood cells was reported on by Leishman [433] in 1905, Hektoen [323] in 1906, Veitch [653] in 1908, and Hektoen [324, 325] in 1908 and 1909, forming the basis for adaptation of this reaction to the study of *Brucella* infection by Huddleson

Infection in sheep and other domestic animals in France was reported by Dubois [182, 183, 184] in 1910 and 1911.

The possible pathogenicity of *Brucella abortus* for man was suggested by Schroeder and Cotton [611, 612] in 1911, a fact which is commonly overlooked in giving credit for early work in the field of human brucellosis of the *abortus* variety They noted that this organism in cow's milk produced a tubercle-like lesion when inoculated into guinea pigs Pasteurization was urged.

Endemic Malta fever in southwest Texas was first reported by Ferenbaugh [213] in 1911 He described 5 cases In the same year, working with Gentry,[251] the isolation of *M. melitensis* from 2

there was still some doubt as to the pathogenicity of the *abortus* variety for man.[123, 143, 623, 610] Hardy and his coworkers,[295] in 1930, stated their belief that *suis* and *abortus* varieties were about equally responsible for undulant fever morbidity.

In 1924 Evans[200] reported on studies of sera from 500 patients, suffering from a variety of diseases, for agglutinins specific for *Brucella melitensis* Fifty-nine (11.8 per cent) gave a definitely positive reaction in dilutions of 1:5 or higher. She considered that these positive reactions were produced as a specific response to *Brucella melitensis* ingested in cow's milk, thereby calling attention to cattle as a possible source of infection.

In 1929 Zanzucchi[733] reported artificial infection of a cow, with subsequent abortion, through injection of *Brucella melitensis* organisms into the jugular vein.

Kristensen and Holm[417] reported the first authenticated instance of infection of the human placenta in Denmark in 1929; *Brucella abortus* was isolated

Castaneda, Tovar, and Velez[133] stated that human cases of brucellosis were suspected by Mexican clinicians soon after the disease was described in the Old World Placeres[533] described isolation of the organism from the blood of a patient in 1923. Gradually it became apparent that the morbidity was high and the disease a serious problem in Mexico Ocaranza and Varela[517] demonstrated bacteriologically the presence of brucellosis in Mexico in 1924

The presence of *Brucella abortus* in cow's milk as a cause of human infection was reported by Carpenter and Merriam[124] in 1926

Isolation of *Brucella abortus* from a human fetus was reported by Carpenter and Boak[116] in 1931, the work having been done in 1927.

Infectiousness of *Brucella melitensis* through unbroken skin was reported by Hardy, Hudson, and Jordan[293] in 1929.

Huddleson and Hallman[359] reported the infectiousness of *Brucella abortus* as well as *suis* and *melitensis* for monkeys in 1929.

Simpson and Fraizer[615] in 1929 and Simpson[625] in 1930 ren-

Fleischner and Meyer first described the intradermal reaction to *Brucella* organisms in 1918.

In 1918 Alice Evans[198] stated: "It is only with great difficulty that *Bact. melitensis* can be distinguished from *Bact. abortus* They are alike morphologically and no difference could be found in their biochemical reaction. The two organisms produce the same results when inoculated into pregnant guinea pigs." She further said: "The very close relationship between *Bact abortus* and an organism pathogenic to human beings adds a new interest to the question of a possible pathogenicity of *Bact. abortus* to human subjects. Considering the close relationship between the two organisms and the reported frequency of virulent strains of *Bact. abortus* in cow's milk, it would seem remarkable that we do not have a disease resembling Malta fever prevalent in this country." She considered the possibility that *Brucella abortus* might be shed in insufficient numbers in cow's milk to produce human disease, adding, however, "on the other hand, are we sure that cases of glandular disease, or cases of abortion, or possibly diseases of the respiratory tract, may not sometimes occur among human subjects in this country as a result of drinking raw cow's milk?"

Meyer and Shaw[457] in 1920 proposed the generic term *Brucella* to include *micrococcus melitensis, Bacillus suis,* and *Bacillus abortus*

Watkins, Warner, and Lake[604] reported an epidemic occurring in Phoenix, Arizona, in 1922.

The intradermal test was further described by Burnet[99] in 1922.

Lake[423] reported the existence of *Brucella* infection in goats in 1922, stating that it had existed in Arizona for at least fourteen years. He pointed to the work of Gentry and Ferenbaugh[251–253] as proving the existence of the infection in Texas for at least thirty-six years. He urged the pasteurization of goat's milk

In 1924 Keefer[390] reported the first case of brucellosis in man known to be due to infection with the *abortus* strain

Other reports soon followed.[124, 248, 361] However, as late as 1930

made by Hardy, Jordan, Borts, and Hardy[295] in 1930 They favored the term *Brucella melitensis, variety melitensis* to designate the goat variety; *Brucella melitensis, variety abortus* to designate the cow variety, and *Brucella melitensis, variety suis* to designate the hog variety. Such a classification avoided the use of such generic terms as *Alkaligenes* but seemed unnecessarily cumbersome. Use of the terms *Brucella melitensis, Brucella abortus*, and *Brucella suis* seems a fortunate end to the controversy.

Brucellosis has been referred to in the literature under as many designations as it has had alleged origins, geographically, characterologically, or based on a similarity to other clinical entities. No purpose is served by naming them all. The following is a partial list: goat fever, dust fever, intermittent typhoid, pseudotyphoid, recurrent typhoid, typho-malarial fever, fecomalarial fever, subcontinuous fever, Mediterranean gastric remittent fever, bilious remittent fever, remittent fever, febrile dyspepsia, recurrent fever, Rock fever, Gibraltar (Malta, Constantinople, Mediterranean, Neapolitan, Cypress, Levant, Cretan, Syriac) fever, sewage, mephytic, or cess-pit fever, new fever

The name "Malta fever" had attracted so much opprobrium that an attempt was made by the International Congress of Medicine and Hygiene and by the Malta Branch of the British Medical Association to completely discourage further use of the term Hughes, after serious consideration for six years, arrived at the designation "undulant fever" Evans pointed out that "the name brucellosis is preferable to all others because it simply expresses infection with *Brucella*, regardless of the nature of the disease response, and because it is applicable to the disease in man or in any of the lower animals" It might be added that this designation deservedly honors Bruce Since it is now known that the chronic disease may exist in the absence of fever, it is obvious that the word "fever" must be deleted from any designation.

dered early reports on the prevalence of brucellosis and its clinicopathologic aspects.

Huddleson, Johnson, and Hamann [361] described the opsonocytophagic reaction as an aid in the diagnosis of *Brucella* infection in man in 1932.

Repeated abortion, with isolation of *Brucella* from uterine discharge, in a human female was reported by Harris [298] in 1934 as a manifestation of the chronic illness.

Monographic treatment of the subject of brucellosis was first done by Hughes [369] in 1897, in his monumental work *Mediterranean, Malta, or Undulant Fever.* In 1930 the concise monograph of Bulmer [97] was published by the Jefferson County Board of Health, Birmingham, Alabama, giving "a summary of correlated facts concerning undulant fever in humans and contagious abortion in animals and the relationship of one to the other from the standpoint of transmission through milk and milk products." In 1931 the United States Public Health Service published the work of Hardy, Jordan, Borts, and Hardy [295] In 1932 Allessandrini and Pacelli [7] published the monograph *Un pericolo sociale· Le Brucellosi,* in Italy. In 1939 Huddleson,[349] with the collaboration of Hardy, Giltner, and Debono, published the first edition of his book *Brucellosis in Animals and Man,* revised in 1943 The first edition of the monograph *Brucellosis (Undulant Fever): Clinical and Subclinical,* by Harris,[302] was published in 1941 Castaneda's [130] monograph *Brucelosis* was published in Mexico in 1942 Purnel's [552] book written in collaboration with Risso and Espasandin, *Brucelosis Estudio de Esta Enfermedad en el Uruguay,* was published in 1944 De la Cruz' [171] monograph *Brucelosis in Cuba* was published in 1946

NOMENCLATURE

Following introduction by their discoverers of the designations for the three strains of *Brucella* as *Micrococcus melitensis, Bacillus suis,* and *Bacillus abortus,* a period of great confusion in terminology resulted A further attempt to clarify terminology was

to include "ambulatory." The terms "silent" and "inapparent" have been introduced and are used by some to designate those in whom infections can be diagnosed definitely (as by positive culture) but who are symptomless. The term "indolent brucellosis" has been used recently by Darley and Gordon to signify the chronic, relatively afebrile illness.

In this monograph the term "acute" is used to designate brucellosis of sudden or gradual onset, with relatively high fever, of any duration. By "chronic" brucellosis is meant a case of insidious onset, long duration, and slow progress, attended by low-grade fever or by no fever. It may clarify terminology further to refer to the acute or chronic *phase*, or *stage*, of the disease rather than to apply either term to the illness itself

It is suggested that the terms "silent," "inapparent," "latent," and "quiescent" infection be reserved for those who harbor the infection with no apparent impairment of health, and that the classifier be ready to reclassify them as chronic brucellosis or acute brucellosis if and when their status changes to one that is no longer symptomless.

By "subclinical" a somewhat different concept is held by the author than the usual dictionary meaning of the term. Stedman's definition is· "Noting a period prior to the appearance of manifest symptoms in the evolution of the disease." Dorland defines the term as· "Without clinical manifestations, said of the early stages of, or slight degree of, a disease" These definitions might be modified and combined, so far as brucellosis is concerned, to indicate a slight degree of the disease, often without definite or readily recognizable manifestations. Patients may remain in this phase for months to years, before or between clinical degrees of illness.

Convalescence from acute brucellosis is still more difficult to define, for this stage may not be convalescence at all, but a chronic illness between acute exacerbations, or chronic or subclinical illness that may last indefinitely

Chronic brucellosis as a clinical entity has become recognized

Definition and Terminology

Hughes defined undulant fever as "an endemic pyrexial disease, occasionally prevailing as an epidemic, having long and indefinite duration, an irregular course, with an almost invariable tendency to undulatory pyrexial relapses." This must be changed to embody the idea that it may be acute or chronic, febrile or afebrile, of long or short duration. The concept must be included that the organism may attack almost any of the tissues of the body, producing more or less characteristic lesions, in the presence or absence of a host of localized or systemic manifestations.

It also involves more accurate use of the terms "acute" and "chronic." According to Dorland, acute means: "(1) Sharp, poignant; (2) having a short and relatively severe course, not chronic." According to Stedman, acute means "(1) Short; (2) clever; (3) of short and sharp course, not chronic" Dorland defines chronic as: "Long continued; not acute." Stedman defines chronic as: "Of long duration, noting a disease of slow progress and long continuance."

Various writers have used the terms interchangeably, with consequent confusion Some designate as an "acute" illness any severe febrile episode, regardless of duration Others consider an illness of more than three months duration as "chronic," regardless of severity. "Acute" often is used to describe the exacerbations or relapses, without regard to the previous existence of a low-grade, long-continued chronic illness "Chronic" is equally as likely to be used to describe the entire illness because of its duration alone Severity of illness and height of fever may be the only criteria. The term "chronic" illness may be reserved by some for only those patients never bedridden with high fever Some apply the term "ambulatory" as synonymous with chronic illness Some writers use the terms "ambulatory" and "subclinical" synonymously. Infected persons, without complaint, may be designated by some as "subclinical" "Latent" or "quiescent" are often used as other synonyms for "subclinical" and even may be extended

Chapter II

ETIOLOGY

Bacteriology

THE generic term *Brucella* includes the three species of the organism, *Brucella abortus, Brucella melitensis,* and *Brucella suis* *Brucella* organisms are very small, nonsporing, non-acid-fast, usually nonmotile, usually nonencapsulated, Gram-negative bacilli or coccobacilli, which grow very poorly on ordinary media and usually develop very slowly when first isolated from the tissues The three species are so closely allied that it may be a problem for the well-trained bacteriologist to differentiate them by any or all methods. Strain variations of each species occur.

Brucella abortus, melitensis, and *suis* all are pathogenic for man, producing similar or identical disease entities but perhaps varying in their severity and, in some degree, in their manifestations *Brucella suis* and *melitensis* usually are more invasive and more virulent than *abortus* The species may usually be identified by its morphologic and cultural characteristics, manner of growth, CO_2 requirements, formation of H_2S, cultivation in the presence of dyes, agglutinin-absorption test, cross-precipitation study, and other measures to be described (Table I)

Brucella melitensis was the first of the group to be isolated, [87] it was thought to be a micrococcus and was named *Micrococcus melitensis* Its habitat is in goats and sheep and it has been found in other animals, including cattle *Brucella abortus* was the next to be identified [35, 38] Its habitat is in cattle, but it has also been isolated from other domestic animals, including goats, hogs, etcetera

by clinicians and allied workers all over the world, whereas until only about a decade ago only the acute variety was recognized by the great majority. In Argentina, Villafañe Lastra[634, 636] has written extensively on the various phases of the subject, including the chronic illness. The concept that brucellosis is *always* a chronic disease was expressed by Goobar.[264] Whether or not the organism always becomes entrenched in tissues or intracellularly or whether it actually may be eradicated completely in some patients, allowing of cure after but perhaps a single acute episode, remains to be proved.

Brucella suis was first isolated from the fetus of a sow.[673] It is a parasite of pigs, with a special pathogenicity for the reproductive organs; it is also found in cattle and other animals.

Morphology

All three organisms are short and slender bacilli, with straight axis, rounded ends, sides parallel or convex outward, 0.6 to 1.5 microns long and 0.5 to 0.7 microns wide (Topley and Wilson [661]). According to Jordan and Burrows,[330] the organism may vary from 0.4 to 3.0 microns, and according to Zinsser and Bayne-Jones,[739] from 0.5 to 2.0 microns. Short forms may be mistaken for cocci (Fig. 1). During division they may be thought to be diplococci. Their usual arrangement is singly or end-to-end in pairs; sometimes they are seen in small groups or short chains. When arranged in pairs their long diameter is in the same axis as that in which they are lying, whereas Gram-negative diplococci usually are found with their long axis at right angles to that in which they are lying. *Brucella* organisms are smaller than any of the Gram-negative true cocci (Fig. 2).

Brucella melitensis usually is more coccal in morphology than *Brucella abortus*, retaining its coccal shape on all media. However, some strains of *Brucella melitensis* may show bacillary forms with a few scattered coccoid forms (Huddleson),[349] and may vary from 0.4 to 2.2 microns in length and from 0.4 to 0.8 microns in width.

Brucella abortus is less variable as to size and shape than *melitensis*, varying in length from 0.4 to 2.5 microns and in width from 0.4 to 0.6 microns (Huddleson). Length may be as great as 3 microns (Topley and Wilson). Whereas usually it is a short rod, coccoid forms may occur occasionally, outnumbering the rods (Huddleson).

Brucella suis apparently always occurs as a rod form, varying from 0.6 to 3 microns in length and from 0.4 to 0.8 microns in width (Huddleson).

TABLE I

BEHAVIOR OF THE VARIOUS SPECIES OF *BRUCELLA* *

Species	*Habitat (usual)*	*Patho-genicity for man*	*Rapidity of growth*	*Growth in absence of extra* CO_2	*Formation of* H_2S	*Growth in presence of dyes*		*Anti-genically (agglutinin absorption test)*
						Thionin 1:100,000	*Basic fuchsin 1:100,000*	
Melitensis	Goat (also sheep, swine, etc)	4+	2+	Yes	None (or trace) in 4 days	Yes	Yes	Melitensis
Abortus	Cow (also goat, horse, etc — *not* swine) †	2+	2+	No	Much (for 2 days only)	No	Yes	Abortus
Suis	Swine (also cow, etc)	3+	3+	Yes (usually)	Much (for 4 days)	Yes	No	Abortus

* Modified from Topley and Wilson [667]

† Isolation of *Brucella abortus* from the submaxillary lymph nodes of hogs has recently been reported (McCullough, N B , Eisele, C. W , and Pavelchek, Emma, Public Health Reports 64 537, 1949)

Staining

The three organisms stain fairly well with ordinary dyes; occasionally the staining is irregular and sometimes bipolar. They are



Fig 2 Photomicrograph, *Brucella abortus* suspension, ×1830

Gram-negative, and usually noncapsule-forming (Capsule formation is discussed on page 22)

Dissociated Forms

Paramelitensis, parasuis, and *para-abortus* are rough variants of the smooth forms Dissociation into rough or "para" forms was

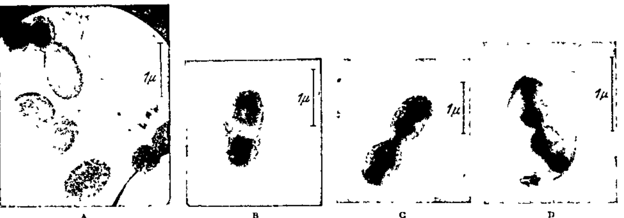


Fig 1 Ultramicroscopic views of *Brucella abortus.*

A Coccus-shaped and elongated oval bodies with clearly visible capsule Probable beginning of division in one organism (×13,500)

B Shortly before division (×14,200)

C Dumbbell-shaped internal body, probably shortly after division (×13,000)

D Same shape of internal body, somewhat later than C (×18,500) (After von Borries, Ruska and Ruska, Year Book of General Medicine, 1938 Courtesy of the Year Book Publishers)

rectly or after mouse passage. Five other strains showed serologic and cultural characteristics similar to the encapsulated strain, without producing demonstrable capsules. With few exceptions, the organism showing characteristics of encapsulated organisms had been isolated from cases of Hodgkin's disease. Those which showed characteristics of nonencapsulated organisms had been isolated from cases of brucellosis. Encapsulated strains were not agglutinable in ordinary antiserum but were highly agglutinable in serums prepared against homologous organisms, and vice versa. The encapsulated strains served as poor antigens, in vivo. Encapsulated organisms could be denuded by cultivation in beef extract broth. These stripped variants were ultimately indistinguishable from the encapsulated forms and produced agglutinins for the encapsulated forms in high titer. Injection of encapsulated forms in rabbits was followed by low phagocytic response while the injection of nonencapsulated organisms produced a high phagocytic response for homologous organisms. Hiss' method of capsule staining was used Mickle considered it possible that these encapsulated *Brucella* may correspond to the "*para-abortus*," "*paramelitensis*," and "*parasuis*" strains discussed by Nègre and Raynaud,[609] Huddleson [350] and others, so named principally because of their inagglutinability in ordinary antiserum. (Figure I shows ultramicroscopic views of encapsulated *Brucella abortus*.)

Inability to confirm all of Mickle's findings was reported by Huddleson,[350] after studying 5 of his atypical cultures. Huddleson preferred a drawing-ink method of staining encapsulated *Brucella*. He considered only the smooth and intermediate forms of the species of *Brucella* were shown to possess a capsule and that the virulence of a given strain is determined by the presence of a capsule and its size

Capsule formation of *Brucella suis* and *melitensis* organisms isolated from the lymph nodes and blood of 10 patients with Hodgkin's disease was recorded by Wise [113] They differed from the usual laboratory strains

first described by Nègre and Raynaud[509] in 1912, using the agglutinin-absorption method for their identification.

These rough or para strains produce antibodies less readily and are not pathogenic for experimental animals. Huddleson[349] stated that *Brucella abortus* and *suis* also become dissociated when they produce a pellicle growth in broth and that *Brucella melitensis* often undergoes spontaneous dissociation when grown on agar slants; once becoming unstable, it seldom, if ever, reverts completely to the normal form (p. 32).

For a complete study of dissociation of *Brucella*, the reader is referred to Plastridge and McAlpine,[534] to Henry,[329] and to Huddleson.[349]

Mucoid or Waxlike Phases

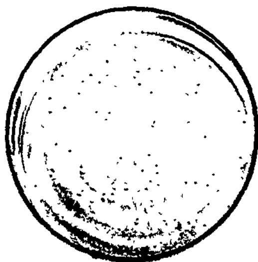
A mucoid growth of the three species of *Brucella* in liquid medium was described[534] in 1930. Henry noted mucoid characteristics in one of five dissociated colony phases of *Brucella abortus* in 1933 Huddleson[353] in 1946, pointing out that *Brucella* dissociates as easily and with as complex a dissociation pattern as that of any other microorganism, described three mucoid phases obtained from *Brucella abortus*, two from *Brucella suis* and one from *Brucella melitensis* He found that one mucoid phase of *Brucella abortus* and those of *Brucella suis* gave rise to daughter colonies which were similar in many respects to S (smooth) phase colonies The mucoid (M) and mucoid daughter (Md) phase cells produced specific growth-inhibiting antibodies in high titer when injected into guinea pigs, rabbits, or cattle and engendered in guinea pigs a high degree of active immunity against experimental infection with that species of *Brucella*, without being pathogenic for guinea pigs or cattle Studies dealing with the immunizing potentialities of these mucoid phases were being carried on

Capsule Formation

Capsule formation was studied by Mickle[483] and others. Five of 27 strains studied produced demonstrable capsules, either di-

viscous sediment that is easily disintegrated on shaking. In shake tubes growth occurs in a band below the surface.

Growth on gelatin is poor and does not produce liquefaction.



BRUCELLA ABORTUS

Fig 3 Discrete, small, round, opalescent, translucent colonies of *Brucella abortus* on tryptose agar plate

Brucella organisms do not produce indole and do not cause gross fermentation of carbohydrates [739] Glucose utilization is controversial No appreciable difference in dextrose utilization is shown by the three species [742] They produce no change in the reaction of milk [739] (Huddleson states that litmus milk is turned slightly alkaline) [201] Nitrates and nitrites are reduced in a semisolid medium.[741] Nitrogen gas from a nitrate medium is produced by *Brucella suis* [201] Ammonia is produced by *melitensis* to a greater

Cultural Characteristics

Growth is usually slow. *Suis* strains usually give the best growth, *melitensis* next, *abortus* the slowest. The cultural characteristics of all three species are similar except for varying CO_2 requirements.

Brucella melitensis is always aerobic but some strains are apparently benefited by extra CO_2.

Brucella abortus requires an atmosphere of from 5 to 10 per cent increased CO_2 tension when freshly isolated from blood, urine, exudates, tissues, milk, and other naturally occurring sources unless the strain has previously been adapted to aerobic growth. *Brucella abortus*, strain 19, does not require CO_2.

Brucella suis is aerobic and may be inhibited by CO_2. However, growth from infected blood in liquid medium is greatly accelerated by an atmosphere containing 10 per cent of CO_2.[201]

On agar the colonies of all three species are small (from 2–7 mm. in diameter), spheroidal, opalescent, translucent, and undifferentiated (Fig 3) They usually are not visible for two or three days or more On liver infusion agar or bacto-tryptose agar slants, the growth has a moist, greasy appearance when viewed from the top[201] (Fig 4) Agar slants inoculated with most strains of *Brucella melitensis* and some strains of *Brucella abortus* may show a brownish color extending down into the medium On potato slants a yellowish color develops in two or three weeks, changing toward a brown or chocolate color, the depth of color varying with the strain, the pigment spreads through the potato

In flasks of broth growth of all three species is slow, clouding of the broth being noted in the first few days. Some strains of *melitensis* give rise to fairly dense turbidity, a moderately heavy deposit, and a granular, usually incomplete surface growth. *Suis* and CO_2-sensitive *abortus* strains give rise, in one to three weeks, to mealy or scaly surface pellicle and a heavy deposit which is difficult to disintegrate by shaking Aerobic strains form no pellicle but produce uniform turbidity and a slight powdery or

Methods of Differentiation of Species

AGGLUTININ-ABSORPTION TEST

This test is useful in distinguishing *Brucella melitensis* from that caused by either the *suis* or *abortus* strains. It will not distinguish between the *suis* and *abortus* strains themselves. It was first described by Feusier and Meyer,[216] and later modified by Evans When the organism cannot be isolated and identified by the bacteriostatic reaction to dyes, the blood serum of the patient can be used for the agglutinin-absorption test It is applicable to any serum which has a titer of 1 . 160 or higher. The technic described by Evans [199, 202] is as follows:

The cultures used as absorbing antigens were #456 of the *abortus* variety and #428 of the *melitensis* variety. They were grown on 1 per cent glucose agar in Blake bottles Each bottle was inoculated with the entire growth from one agar slant suspended in about 1.5 cc of saline solution After forty-eight hours incubation the growth was washed off with about 15 cc of physiologic saline solution containing 0 5 per cent formalin, by rocking the bottle in the hand After standing in the refrigerator for a few days, the dead bacterial suspension was centrifugalized, the clear supernatant fluid was discarded and saline solution containing 0 5 per cent formalin was added to restore the original volume. This suspension was then standardized to a density equivalent to 20,000 parts per million of the silica standard

In their earlier studies (1925) it was found that an antigen of a density of 60,000 p p m would absorb all homologous agglutinins from a serum with a titer of 1·640 when the absorption was carried out in a 1 5 dilution of the serum; an antigen of half of that density would absorb all homologous agglutinins from a serum with a density twice as high In this study an antigen of a density of 60,000 p p m. was always used to absorb serums of a titer of 1 640, and the density of the antigen was reduced proportionately to absorb serums of lower titer Serums of higher titer were diluted to a titer of 1·640 and the diluted serum was absorbed with an antigen of a density of 60,000 p p m The procedure was as follows·

degree than by *suis* and *abortus*.[201] Hydrogen sulfide is produced in abundance by *Brucella suis*, to a lesser degree by *Brucella abortus*, and to a very slight degree, if any, by *Brucella meli-*



Fig 4 *Brucella abortus* on tryptose agar slant

tensis,[201] differentiation of species by this property is described on page 29.

CULTURAL METHODS

Methods of isolation of *Brucella*, including animal inoculation, are discussed under Diagnosis (pp 294–311).

when newly isolated bovine strains are suspected. Differentiation is accomplished by the following circumstances At the end of the period of incubation it will be found that *abortus* strains have grown only on the medium containing fuchsin; *suis* strains have grown only on the medium containing thionin, *melitensis* strains have grown on both media but less luxuriantly than the other two species. Topley and Wilson [647] stated that the dye-differentiation method is the most useful but must not be relied on alone

Brucella abortus, strain 19, the cattle-immunizing strain, is more sensitive to thionin, methylene blue, and thionin blue (British Drug House, London) and can be differentiated from the other *abortus* strains by determining a critical dye level in the medium which selectively inhibits it.[436] Stock solutions of thionin and methylene blue deteriorate on standing but thionin blue remains stable over a period of two months. Strain 19 was inhibited at a dye threshold of 0 5 mg of thionin blue per liter of tryptose agar (Difco) whereas virulent strains grew well at that level, being inhibited only at dye concentrations ranging from 0 7 to 3 0 mg. per liter.

PRODUCTION OF H_2S

Production of H_2S may be determined by the method first described in 1927 [357] The method now in use is as follows [349]

A lead acetate solution is prepared by dissolving 10 grams of normal lead acetate (C P) in freshly boiled distilled water A good grade of filter paper is immersed in the solution until it is thoroughly saturated It is then removed, allowed to dry, and cut into small strips The paper is stored in a stoppered bottle until ready for use. When H_2S determinations are to be made, liver agar slants, prepared from liver infusion which has previously been treated with one-half volume of ether at room temperature for three days and from which the ether has been removed in a separating funnel, are planted heavily from a forty-eight- to seventy two hour growth A strip of the lead acetate paper of sufficient length is placed inside the tube beside the cotton plug so that the paper will extend about one inch below it. One should make certain that the cotton plug is not moist and does not contain

An equal quantity of glycerin is added to the serum in the field before sending it to the central laboratory. It was found that the test required 1.4 cc. of the serum-glycerin mixture to give sufficient absorbed serum of 1:5 dilution for the test. It requires 10.5 cc. of the stock antigen to obtain an antigen of a density of 60,000 p.p.m. to absorb the serum in a 1:5 dilution. The tube containing 10.5 cc. of the stock antigen was centrifugalized, 8.4 cc. of clear supernatant fluid was removed and 1.4 cc. of the serum-glycerin mixture added to the remaining 2.1 cc. of antigen. Sediment was emulsified and the tube was then placed in a water bath at 37° C. After four hours it was removed to the refrigerator. The next day the tube was again centrifugalized and the agglutinin titer of the clear supernatant fluid was determined by testing with both the *abortus* and *melitensis* antigen. For this test 0.5 cc. of an antigen of a density equivalent to 500 p.p.m. of the silica standard was added to each of the series of tubes containing the diluted serum.

BACTERIOSTATIC ACTION OF DYES

Huddleson[317] in 1928 suggested using the varying ability of the three strains of *Brucella* to grow in the presence of certain dilutions of thionin, basic fuchsin, methyl violet, and pyronine to distinguish between them. Since then the test has been standardized, using thionin and basic fuchsin only. The dyes should be certified, as made by the National Aniline and Chemical Co., Inc., or should be standardized against them. Liver agar originally was used with these aniline dyes incorporated; bacto-tryptose agar containing a final dilution of thionin or basic fuchsin of 1:100,000 has been found more satisfactory for the purpose. Huddleson[317] recommends that the dyes be freshly prepared in a 0.1 per cent stock solution with sterile distilled water every sixty days. The dye suspensions are heated in flowing steam for twenty minutes, shaken well, and while still hot added to the melted medium before it has time to cool, thus resulting in a uniform distribution of the dyes in the medium. The plates are inoculated with loops of the heavy suspension of a forty-eight- to a seventy-two-hour agar slant growth and then are incubated aerobically at 37° C. for seventy-two hours or in 10 per cent CO_2

of *abortus* cells. It was found to contaminate the polysaccharide C_1 fraction from which it was separated with difficulty, and produced a nonspecific skin reaction in infected or uninfected individuals, persisting for about twelve hours, when used in a dilution of 1:200. When diluted to 1.100,000 it precipitated antiserum from one of the species of *Brucella*.

The fat and phosphatide fractions constitute an important specific difference in the three species[201] The fat fraction increases in the order of *Brucella abortus*, *Brucella suis*, and *Brucella melitensis*, the phosphatide fraction decreases in that order.

REDUCTION OF NITRATES AND NITRITES

Distinction between the three species may be made by determination of the reduction of nitrates and nitrites.[741] A semisolid medium consisting of peptone 2 0 Gm, beef extract 1 0 Gm, sodium chloride 3 0 Gm, agar 2 0 Gm. in 1000 cc. of distilled water, adjusted to a *pH* of 6.8, was inoculated with organisms of each species. On addition of 0.2 per cent potassium nitrate to the medium, *abortus* and *suis* grew dispersed throughout the medium instead of only in the limited zones from 2 to 6 mm below the surface. *Suis* destroyed 0 05 per cent potassium nitrate in five days, while *abortus* and *melitensis* did not *Melitensis* strains usually reduced nitrites more actively than did *abortus* In mediums containing 0 2 per cent each of potassium nitrate and potassium iodide, *suis* evolved an abundance of nitrogen gas with rapid disappearance of nitrates and nitrites, while *abortus* rarely liberated gas *Melitensis* and Danish *suis* strains failed to generate gas *

QUANTITATIVE CROSS-PRECIPITATION STUDIES

By means of quantitative cross-precipitation studies, using goat antisera, the three endo-antigens of *Brucella* were found serologically distinguishable[525]

* For complete studies on the chemical constitution and biologic properties of *Brucella* organisms, many of which are still controversial, the reader is referred to standard texts on bacteriology, to Huddleson's monograph, *Brucellosis in Animals and Man* and to journals on experimental laboratory procedures

dried agar, thus preventing a partial anaerobic condition inside the tube The tubes prepared this way are incubated at 37° C. for twenty-four hours. The paper is then removed, numbered and preserved A fresh piece of paper is placed in the tube in the same manner as the previous one and the same procedure followed This operation is continued for four successive days. One may then determine, by comparing the extent of blackening or formation of lead sulphide on the four strips of paper, the group to which the strain in question belongs. If a given strain continues to produce H_2S to a considerable degree for a period of four days, it belongs to the *suis* species. [This does not hold true for those strains of *Brucella suis* isolated from swine by Thomsen in Denmark The *suis* strains which he isolated produce little if any H_2S during a four-day period.] If the strain produces a considerable amount of H_2S for only two days, it belongs to the *abortus* species When no H_2S or only a trace is produced during this period, the strain is *Brucella melitensis*.

CATALASE ACTIVITY

The virulence of each of the three species of *Brucella* is directly associated with the activity of the enzyme catalase contained in live cells.[367] The *suis* strain contains the largest amount of catalase and is the most active, the *melitensis* strain contains the next largest amount of catalase and exhibits the next greatest activity, the *abortus* strain the least. This observation applies to smooth or dissociated forms alike[367] Rough strains of *melitensis* and those of low virulence show about the same activity as *abortus* cultures of high virulence. It is therefore essential to determine the species to which a given culture belongs before attempting to correlate the virulence with the action of the enzyme

CHEMICAL DIFFERENCES

The polysaccharide fraction varies in the relative amount and character of the C_1 and C_2 components as the most notable chemical differences in the three species[349] The C_1 fraction found only in *suis* and *abortus* is nondialysable When freed from nitrogen-containing substances they are found to be biologically inactive. An S fraction was extracted from the albuminoid fraction

alent to a 1 centimeter on the Gates apparatus, is mixed with whole citrated blood of nonimmune and noninfected individuals and incubated at 37° C for thirty minutes, in accordance with the usual technic for doing the opsonocytophagic test as a diagnostic procedure (p 313). With such a partially dissociated culture, the neutrophiles ingest the bacteria in varying numbers Bacteria from a smooth culture of *Brucella* are phagocytosed only to a slight degree, or not at all, by neutrophiles in "normal" blood

MUTABILITY OF BRUCELLA

Taylor, Lisbonne, and Roman [659] reported recovery of many *abortus* and few *melitensis* strains from cattle, of only *melitensis* strains from goats, and a *melitensis* strain from 11 of 12 sheep, the remaining one typing as probably *abortus*. They suggested that mere passage of a strain through an animal of another species does not affect the fundamental characteristics of the established variety, and that if a change from one established type to another does occur, some more complicated process is required, such as long-repeated passages in a foreign animal species or the interplay of antigens and immune bodies of different varieties of *Brucella* in the host

Wilson and Evans [710] reported the apparent mutation of *Brucella melitensis* to *Brucella abortus* by passage through a pregnant heifer. However, they could not reproduce the apparent result in a subsequent experiment in which four pregnant heifers were similarly inoculated The persistence of a previously unrecognized *abortus* infection, with suppression of the *melitensis* strain used for experimental inoculation, could account for the unique result obtained.

RESISTANCE

Resistance of the various strains of the three species show variations dependent on origin and conditions [75, 114, 103, 261, 383, 510, 661] *Brucella melitensis* survived for six days in urine, for sixteen days on a cover slip, for six weeks in dust, for forty-three to seventy-two days in soil, for seventeen to sixty-nine days in manured soil,

THERMOAGGLUTINATION REACTION

Burnet [100] described a method of heating an emulsion of the culture in a water bath at 90–100° F, noting that rough strains will precipitate out Staub [649] considered the method reliable, stating that the phenomenon occurs often in from five minutes to an hour. Huddleson [349] stated that studies conducted on a large number of strains for a period of four years showed that the test cannot be relied on as a constant means for detecting dissociated forms; very often a strain found heat-agglutinable in one trial passed through several successive trials before it again manifested this phenomenon

AGGLUTINATION WITH BASIC FUCHSIN

The cells from an agar slant growth are suspended in a 1:2000 dilution of basic fuchsin in distilled water which is incubated for two hours at 37° C. All unstable strains are said to be agglutinated in varying degrees at the end of two hours, while normal ones remain uniformly suspended [175] Huddleson [349] considered that it gave inconstant results, although "far superior to and much more delicate than the thermoagglutination test."

AGGLUTINATION WITH TRYPAFLAVINE

Alessandrini and Sabatucci [8] described a method of suspending *a forty-eight-hour culture in physiologic salt solution* to a turbidity of 1 by the McFarland nephelometer Equal parts of the bacterial suspension and the 1 1000 dilution of trypaflavine are mixed in a small test tube and incubated at 37° C for six hours If the culture is a variant, agglutination will be observed, a normal or smooth culture is not agglutinated.

OPSONOCYTOPHAGIC REACTION

Use of this reaction for the detection of antigenic variants of *Brucella* was described by Munger and Huddleson [503] as more satisfactory than the thermoagglutination and the dye-agglutination tests. A suspension of *Brucella*, partially dissociated, equiv-

found to be killed by temperatures of 143 6 to 145.4° F. in three minutes, using the standard pasteurizing units.[504]

PATHOGENICITY

All three strains of *Brucella* are infectious for man, their infectiveness apparently decreasing in the order named—*melitensis, suis,* and *abortus* The degree of infectiveness is subject to wide variations in all three species, being modified by as yet ill-understood factors Mazza [465] felt that *Brucella* infections are changing from a septicemia-producing organism to one attacking various organs.

Brucella melitensis produces infection mainly in *goats* and *sheep,* sometimes resulting in abortion but usually in a chronic disease. However, abortion may occur in 50 to 90 per cent of the animals when a herd of goats is first infected.[184] *Brucella* infection in sheep, widespread in France and elsewhere, has been almost unknown in the United States and Canada, but is slowly becoming recognized. Cows infected by *Brucella melitensis* do not ordinarily abort but the organisms may be excreted in their milk, with resulting infectiousness of the milk. *Swine* were suspected of transmission of *melitensis* infection in Iowa in 1945.[384] In February, 1946, *Brucella melitensis* was isolated from the tissues of 12 of 20 gilts.[72] (Huddleson, cited by Jordan and Borts, stated that *melitensis* was isolated from aborted fetuses of infected sows in Malta in 1938) *Cats* infected with *Brucella melitensis* are likely to show no clinical evidence of illness.

Brucella abortus is infectious for the cow as well as for many other animals, they may abort [515] *Sheep, goats, horses, dogs, rats, guinea pigs, cats,* and *chickens* and other *birds* are known to be susceptible *Swine* are thought to be insusceptible and not to transmit *abortus* infection * The major localizations of infection in the *cow* are the pregnant uterus, the placenta, and the udders. The testes may be involved in the bull

Brucella suis is infectious for *pigs,* often producing abortion in these animals *Cows* may be infected, excreting the organism in

* But see footnote, Table I, page 18.

for eighty days on dry fabric, for six to seventy days in water, *for twenty-five days in sterilized sea water, for twenty days in dry* sterilized sand, and for only a few hours in sunlight. *Brucella suis* from naturally infected hog spleens survived more than thirty days when refrigerated at −10° F. and for four to forty-five days when kept in meat-curing brine. *Brucella abortus* was isolated [86] from infected exudate from a cow's uterus stored in an ice chest for seven months. Bosworth [75] reported isolation of *Brucella abortus* from an infected bovine fetus after one hundred and eighty days. Thompson [664] stated that the ice cream made from naturally infected milk, stored at 32° F. allowed recovery of the organism thirty days later. Butter yielded *Brucella abortus* after storage at 8° C. for one hundred and forty-two days and Roquefort cheese yielded *Brucella* after two months [114]

Brucella organisms show the usual susceptibility to moist heat and disinfectants, being destroyed in ten minutes at 60° C. and in fifteen minutes in 1 0 per cent phenol. They survive in low temperature, however, a month or longer at 0° C. *Brucella suis* survives even lower temperatures than do the other strains of *Brucella* and for longer periods of time. *Brucella abortus* and *Brucella suis* are killed in three minutes at temperatures from 143 to 145° F.[380]

Acid production in raw milk at room temperature kills *Brucella* "fairly rapidly." [607] *Brucella* disappear within ten days in milk, and the organisms survive two hours or more in milk mixed with gastric juice [380] Although it has been stated that the organism is rarely present for more than a few days in butter and cheese made from sour milk, these findings are subject to revision in the light of present knowledge In butter and cheese made from fresh milk, the organism may survive for three months or more (*See chapter on Epidemiology*)

Pasteurization at usual temperatures is effective in killing the organism in milk *Brucella melitensis* and *abortus* are killed at 140 to 142° F. for fifteen minutes All three species are destroyed at 145° F. in nineteen minutes.[75] *Brucella abortus* and *suis* were

found to be killed by temperatures of 143 6 to 145.4° F. in three minutes, using the standard pasteurizing units[504]

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All three strains of *Brucella* are infectious for man, their infectiveness apparently decreasing in the order named—*melitensis, suis,* and *abortus.* The degree of infectiveness is subject to wide variations in all three species, being modified by as yet ill-understood factors. Mazza[465] felt that *Brucella* infections are changing from a septicemia-producing organism to one attacking various organs.

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* But see footnote, Table I, page 18.

milk. Other animals, such as *horses, dogs,* and *fowl* are less often infected. *Swine* do not readily produce agglutinins in high titer;[355] they may carry the organism for years without showing agglutinins in titers above 1:10. *Suis* infection in the *cow* has repeatedly produced severe epidemic brucellosis in human beings who have ingested the raw infected milk (p. 87). *Cats* have been reported to abort following *Brucella suis* infection.

Knowledge is still far from complete as to the pathogenicity of the three species for various animals.

The disease is becoming chronic in domestic animals, only one-third to one-half of infected cows ever fully recovering.[205] Schmidt[609] stated that the organism, at least in cattle, has become less virulent and that the incidence of acute brucellosis, both in cattle and man, is decreasing because of its attenuation. He compared the situation to that occurring in syphilis in the fifteenth century when there was high fever and early death, however, in about fifty years, syphilis assumed a chronic form. He felt that the disease, when chronic in cattle, is likely to be transmitted as a chronic illness to human beings. Huddleson,[355] however, stated that he has noted greater virulence steadily during the past thirty-one years.

Of the laboratory animals, the guinea pig is most susceptible to infection with all three species. Rabbits, rats, mice, and monkeys may be infected. The lesions produced by parenteral inoculation in guinea pigs are variable in size and number and may not be visible macroscopically. *Brucella* organisms do not ordinarily produce a lesion at the site of invasion. The passage through the intestinal mucosa, their usual portal of entry, is followed quickly by the transportation to the mesenteric lymph nodes from which they pass into the blood stream, this passage takes place in about thirty minutes in the guinea pig. When the organisms enter through the traumatized skin, a specific local lesion accompanied by a secondary reaction in the regional lymph nodes may be produced. The entry of the organisms through the tonsils and other buccal lymphoid tissue was considered a possibility.[229]

The separate species of *Brucella* cannot be determined accu-

rately from the study of tissues of inoculated laboratory animals. If the animal is killed at the end of six weeks there may be local abscesses, pale bloodless hyperplasia of the regional and distant lymph nodes, variable degree of enlargement of the spleen which may contain necrotic foci, similar foci in the liver, and sometimes bone and joint abscesses. The organism is recovered most readily from the glands, spleen, and bone marrow. The blood-agglutination test is usually high, a titer of 1:25 or higher being considered suggestive by most workers.[667] The presence of agglutinins in the blood and, more important, the culture of the organism from the tissues, constitute the most reliable diagnostic indices from laboratory animal inoculation

Strain 19

Noting that Strain 19 has been used for the vaccination of cattle since 1938 and that cultures of *Brucella* which will grow in the absence of CO_2 are recently being recovered from cattle, Huddleson[355] expressed the thought that these may be of that origin. He expressed the certainty of the pathogenicity of this strain for man, pointing to infection of veterinarians (p 516)

Chapter III

EPIDEMIOLOGY

Infectiousness and Methods of Transmission

There is little evidence that the *Brucella* infection is transmitted to human beings by any important means other than the ingestion of infected raw milk or other unpasteurized dairy products, contact with infected animals or their flesh or products of conception, or contact with live cultures during the course of scientific work.

POSSIBLE INFECTIOUSNESS OF HUMAN BRUCELLOSIS

In no instance has the author seen two members of the same family *acutely* ill with brucellosis at the same time. No special precautions against contagion were taken. Cases of multiple acute cases in one household have been reported but always in the presence of an outbreak in which the infection has been traced to an infected milk supply and, in one instance, to an apparently contaminated water supply. Occupational exposure could account for multiple cases if more than one member of the household were so employed Bruce stated that, although cases of brucellosis were scattered through the various wards in a hospital, there was no evidence that the disease was communicated to other patients.

One of the author's patients failed to infect her husband although, following a recent abortion, she had a profuse uterine discharge from which *Brucella* was isolated. No precautions were taken against infection during sexual intercourse Four years

later the husband developed a Brucella infection of the skin (*Fig. 36E*) which began in abrasions of the fingers incurred during slaughtering of infected cattle, suggesting that he did not possess natural immunity. Animal strains may be more infectious than human strains.

On more than one occasion the author handled the placentas of patients who aborted during the course of brucellosis (in one emergency with ungloved hands) with apparent impunity, although the placentas were grossly infected. This may indicate a natural immunity such as some persons exhibit when ingesting infected milk, or an organism of low virulence, or an infection which remained undiagnosed. Veterinarians, slaughter house employees, dairymen, general farmers, and laboratory workers do not all develop evidence of clinical brucellosis, perhaps for similar reasons

Huddleson and Munger [365] suggested human contact as a possible source of infection in 96 persons in an outbreak which was considered by others to be due to infection of the water supply by back-siphonage from a laboratory sink (p 56).

Kern [398] noted the occurrence of brucellosis in a gynecologist following vaginal examination of an infected patient although the evidence of human origin of this infection seemed slight.

The following case histories are more suggestive but also lack proof of human transmission

A 29-year-old married woman complained in October, 1936, of pain in the left lower quadrant which had begun shortly following delivery three years before, and which had increased in severity in the past three or four days The pain had been worse for a few days before each menstrual flow and was usually relieved at the onset of the menses. She had had amenorrhea for three months at the time of the initial consultation Temperature had ranged from 99 to 100.2° F for several weeks and she had had low back pain and fatigue for about that period

Physical examination showed no evidence of pregnancy but there was definite thickening and tenderness of the left fallopian tube Blood-agglutination reaction with *Brucella abortus* was positive in a 1·20

dilution of the serum Subsequently intradermal reaction with heat-killed *Brucella abortus* organisms was violently positive. Pelvic pain was relieved promptly after the initiation of a series of short-wave diathermy treatments, with vaginal electrode, during which time *Brucella abortus* vaccine therapy was given. Recovery was apparently complete. Two subsequent pregnancies were accompanied by no untoward incident.

A year later, in October, 1937, this patient's husband, a 30-year-old physician, developed an orchiepididymitis. The onset had been gradual. His other complaints were fatigue of about five years duration, much more marked following involvement of the testis and epididymis. Blood-agglutination reaction with *Brucella* was positive in a 1:160 dilution. Intradermal reaction to heat-killed *Brucella abortus* organisms was positive He had the typical pallor of brucellosis. He was referred to a urologist who considered it "most unlikely that involvement of both testis and epididymis could be attributable to *Brucella* infection." He considered orchitis alone a possible complication and ignored the positive blood-agglutination reaction. There was very slow resolution of the process, with no specific therapy Systemic manifestations continued.

It is a matter of speculation as to whether these two genital tract infections in husband and wife were interrelated in the way of direct transmission from one to the other, or whether both were contracted from a common or separate infected raw milk supply. That both infections involved the generative tract may have been coincidence or may have illustrated the intermarital type of infection since referred to by Carrillo-Cardenas.[126]

Other examples of infection in both husband and wife have been noted but always under such average conditions that a common source of both infections could not be ruled out. In one instance the husband had been ill with a chronic infection for several years before coming under observation Culture of prostatic fluid had been positive for *Brucella abortus*. The wife had become ill with brucellosis several years later but without any manifest evidence of genital tract infection The husband felt quite certain that he was responsible for her infection Instead

of reassurance to the contrary, one would be inclined to thoughtful silence under such circumstances in view of the proved presence of *Brucella abortus* organisms in the semen, and the generally accepted theory of transmission of infection by the infected bull and the boar.[78]

The apparently high infection-rate among physicians and nurses and their families may point to infection contracted from their patients and thence perhaps to members of their families. However, in rural regions they are frequently exposed to the use of unpasteurized milk and dairy products Physicians in large urban centers often maintain country places where their own herds may be a source of infection Others may contract infection, as does the general population, through ingestion of raw milk or its products Statistics as to incidence and epidemiology of *Brucella* infection among physicians and nurses are lacking.

The infection-rate in veterinary physicians is known to be exceedingly high (p 65). A higher than average occurrence-rate has been noted by the author in the families of veterinarians This too must be viewed with caution so far as human transmission is concerned since veterinary practice is largely in rural regions where raw milk may be consumed Veterinarians themselves may place too great reliance in negative blood-agglutination tests in cattle, allowing their families to continue to use raw milk from supposedly infection-free herds.

Hardy and his coworkers [295] reported the death of a 27-year-old married woman whose husband had been acutely ill and had been nursed by her During the husband's convalescence she suddenly had become acutely ill Pasteurized milk had been used but the husband had been frequently away from home and could have acquired his infection elsewhere, whereas the wife, as the nurse, may have acquired the infection from the excreta of her husband

In Mexico City, transmission of brucellosis by human contact was considered to be possible but infrequent.[18] It was stated that "the possibilities increase when they practice any sexual aberration which permits the access of *Brucella* to the digestive tract."

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Buser-Pluss[161] reported the illness of a premature baby ill since birth, in whom infection must have been congenital or from mother's milk, only mother's milk or powdered milk having been ingested since birth.

Strong[655] stated: "Another path by which the organism may leave the body is in the milk. In 3 infected women who were examined by the British Commission, *Brucella melitensis* was recovered from the milk of 2 of them."

MILK AND CREAM

Raw milk and cream from infected cows and goats, and dairy products made from them, is the major source of brucellosis in man, except in those occupational groups in whom there is direct contact with animals, their products of conception, or their carcasses, or with live cultures of *Brucella*.

Cow's Milk

In 1930 Traum[673] estimated that approximately 20 per cent of the cattle in the United States were infected and that from 6 to 10 per cent were excreting *Brucella* in their milk. Various other nationwide and local estimates have ranged above and below these figures. The statistics compiled by the Bureau of Animal Industry of the United States Department of Agriculture for the fiscal year 1945 (Table II) list the number of herds tested, number of cattle tested, number of reactors found, and percentage of reactors for 47 states (California not included) and for Puerto Rico.

These figures do not represent the actual percentage of infected cattle. Not included is the number of cattle infected but showing negative agglutinins or agglutinins in low titer only It is conservative to estimate the percentage of infection as at least twice the percentage of reactors

Infection in cattle and therefore in raw milk cannot always be detected by the methods in common use The blood-agglutination reaction in cattle is the only method of detection routinely used It is only through culture of blood and milk and animal inocula-

Campbell[100] has noted the increase in cases of brucellosis reported to the State Health Department of Illinois. He points out that pasteurization of milk has been widespread in Illinois, that Bang's disease in cattle has definitely decreased, that few of the human cases have had contacts with goats or hogs, and concludes that there is reasonable ground for believing that brucellosis can be spread by human contact.

It seems all but impossible to evaluate human transmission since no individual can be proved to be uninfected prior to the suspected human contact, so inapparent and obscure may have been a previously acquired infection. Any depleting illness or injury may precipitate exacerbation of a quiescent infection, which may easily be mistaken for one recently acquired, thus confusing coincidence with cause and effect.

MOTHER'S MILK OR CONGENITAL INFECTION

Congenital infection in infants may be indistinguishable from infection from mother's milk.

The author observed highly suggestive symptoms of brucellosis in two successive breast-fed babies born to an infected mother Both were normal and healthy at birth but pallor, listlessness, low-grade fever, and failure to gain weight soon became evident and persisted for several months. Ultimately both infants recovered Lack of adequate laboratory facilities prevented a proper study of the babies and culture of the mother's milk. More definite evidence of congenital infection of babies or of infection from mother's milk has been presented by Hagebusch and Frei;[285] 26 babies developed clinical and laboratory evidence of brucellosis before they had had any food other than mother's milk Of these, 4 developed relatively severe symptoms and positive blood-agglutination and intradermal tests before nursing and before ingesting any food other than dried or evaporated milk Illness began in from three to eight days following delivery Placental transmission or contamination in passage through the birth canal was suggested.

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Cow's Milk

In 1930 Traum [673] estimated that approximately 20 per cent of the cattle in the United States were infected and that from 6 to 10 per cent were excreting *Brucella* in their milk. Various other nationwide and local estimates have ranged above and below these figures. The statistics compiled by the Bureau of Animal Industry of the United States Department of Agriculture for the fiscal year 1945 (Table II) list the number of herds tested, number of cattle tested, number of reactors found, and percentage of reactors for 47 states (California not included) and for Puerto Rico.

These figures do not represent the actual percentage of infected cattle. Not included is the number of cattle infected but showing negative agglutinins or agglutinins in low titer only. It is conservative to estimate the percentage of infection as at least twice the percentage of reactors.

Infection in cattle and therefore in raw milk cannot always be detected by the methods in common use. The blood-agglutination reaction in cattle is the only method of detection routinely used. It is only through culture of blood and milk and animal inocula-

TABLE II

RECORD OF BRUCELLOSIS (BANG'S DISEASE) TESTING

FISCAL YEAR 1945

	Herds tested	*Cattle tested*	*Reactors found*	*% reactors*	*Reactors held*	*Calves vaccinated*
Alabama	15,291	122,334	5,051	4.1	1,259	6,981
Arizona	1,303	12,377	571	4.6	196	1,571
Arkansas	4,413	55,777	2,846	5.1	327	1,735
Colorado	2,855	25,014	1,353	5.4	1,333	15,437
Connecticut	1,048	34,516	932	2.7	0	1,337
Delaware	*2,192*	*24,855*	*734*	*3.0*	*87*	*2,813*
Florida	5,809	112,160	3,329	3.0	215	5,208
Georgia	7,529	80,816	2,711	3.3	0	403
Idaho	3,779	42,160	2,275	5.4	225	11,250
Illinois	47,698	497,052	26,958	5.4	23,131	41,221
Indiana	1,042	11,200	193	1.7	30	122
Iowa	13,598	166,314	16,031	9.6	0	21,020
Kansas	11,154	104,339	7,634	7.3	0	60
Kentucky	1,090	42,033	1,586	3.8	609	1,645
Louisiana	2,847	28,231	3,009	10.6	674	20,898
Maine	12,833	157,090	6,135	3.9	1,418	5,319
Maryland	7,005	95,176	2,751	2.9	452	16,874
Massachusetts	19	1,001	18	1.8	18	5,365
Michigan	16,906	192,457	6,005	3.1	1,730	4,725
Minnesota	17,868	316,957	12,761	4.0	0	9,441
Mississippi	*6,846*	*57,591*	*2,450*	*4.2*	*0*	*0*
Missouri	6,377	79,303	4,318	5.4	0	0
Montana	2,332	38,224	1,389	3.6	486	10,508
Nebraska	1,639	24,303	883	3.6	0	1,220
Nevada	316	7,520	327	4.3	276	1,848
New Hampshire	13,471	160,063	5,311	3.3	0	4,136
New Jersey	3,458	64,823	915	1.4	335	3,143
New Mexico	2,953	36,587	604	1.6	48	1,148
New York	16,372	328,205	42,192	12.8	41,692	100,372
North Carolina	9,214	131,494	1,250	.9	50	117
North Dakota	7,776	143,978	5,752	4.0	160	11,264
Ohio	11,944	166,932	9,117	5.5	99	7,608
Oklahoma	2,425	53,555	2,311	4.3	436	3,883
Oregon	24,067	213,097	3,781	1.8	18	3,204
Pennsylvania	46,880	574,822	17,574	3.0	0	19,724
Rhode Island	93	2,679	78	2.9	74	429
South Carolina	3,684	37,018	954	2.6	14	217
South Dakota	1,637	25,182	1,973	7.8	818	11,847
Tennessee	2,430	66,699	3,920	5.9	1,503	7,016
Texas	1,012	32,572	788	2.4	0	3,949
Utah	4,603	39,203	1,891	4.8	1,881	10,178
Vermont	10,630	165,253	6,334	3.8	6,332	36,812
Virginia	9,093	129,463	3,220	2.5	78	4,917
Washington	8,463	101,567	4,837	4.8	98	26,108
West Virginia	7,580	96,625	1,150	1.2	0	1,906
Wisconsin	11,013	289,452	15,794	5.4	0	50,386
Wyoming	654	14,308	592	4.1	373	5,454
Puerto Rico	225	11,091	452	4.1	233	1,072
TOTAL	395,236	5,213,458	243,050	4.7	86,738	501,114

tion that *Brucella* may be demonstrated when blood-agglutination reactions are negative. (See pages 508–512.)

A young farmer, suffering from chronic recurrent brucellosis, volunteered the following comment indicating the uncertain status of cattle with negative blood-agglutination reactions "We were using milk from a 'negative' cow and she aborted when she was four or five months along. A neighbor had a cow that was negative on all four counts and within two weeks she lost a calf and abortion then went right through the herd."

Borts[71] stated that brucellosis is the most common milk-borne disease, and that it is the most common disease transmitted from animal to man He considered that both cattle and hogs may remain chronically infected and a source of infection, with the blood-agglutination titers negative or below that considered as suspicious or positive. This cannot be stressed too greatly.

Negative blood-agglutination reactions or reactions in low titers only are found in animals, as in man, in the presence of positive culture from blood, milk, or other sources Doyle and Beckett[191] in 1936 reviewed several reports and cited their own experience in the isolation of *Brucella abortus* from cow's milk in the absence of significant blood agglutinins.

Fitch and Bishop[218] reported on agglutination tests of milk from 67 dairies selling raw milk to a municipality, *Brucella abortus* was demonstrated in 17 or 25.4 per cent. They stated that if agglutinins for *Brucella* can be demonstrated in a 1 . 25 dilution in a test of raw market milk living *Brucella* organisms can usually be found

Infectiousness of unpasteurized milk cannot always be detected by agglutination tests of blood of cattle or of the milk[479] In 3 cows *Brucella* was isolated from the milk but the blood-agglutination reaction remained negative in a dilution of 1:25 on numerous tests, before and after isolation of the organism One cow which had a high agglutination titer in a previous test became negative and remained so but continued to shed the organisms in the milk Of 705 cows with blood-agglutination reactions in titers of 1 200 or higher, 273 or 38.7 per cent showed no agglutinins in their

milk However, the milk of 88 or 32.3 per cent of the 273 yielded *Brucella abortus* on culture. It was not unusual to find cows with a negative agglutination reaction in the milk in which *Brucella* was found on culture. The organism in the udder, and agglutinins in the milk, occasionally were found in the absence of agglutinins in the blood. There was little if any correlation between *Brucella* organisms and agglutinins in the milk.

Winter [112] stated that additional agglutination tests usually will reveal the presence of the disease if early tests are negative. However, milk and other dairy products produced before subsequent tests have been made are just as infectious as from cows with known infection. In fact just such cows would be retained in herds producing raw grade A milk or raw Certified Milk.

Certified Milk

Certified Milk has many supporters because of the efforts made to produce a clean milk that is free from any pathogenic organism, whether raw or pasteurized. There can be no disagreement that pasteurization is not a proper cover-up for faulty methods of production.[41, 85] Instances of infected pasteurized milk have been cited. Breakdown of pasteurizing equipment may go unnoticed or may be ignored. Cows with infected udders or with udders caked with excreta, or with known *Brucella* infection, may be milked and the product sold, raw or pasteurized. Barns may be insanitary and utensils contaminated. No such carelessness is tolerated in the production of Certified Milk so that the claims of the producers that it is superior milk are justified. On the other hand no such carelessness is tolerated in the production of any milk by the large producers Offenders are few and scattered Pasteurization technic is frequently checked in all states having proper milk ordinances and supervision. Means of detecting imperfect pasteurization by the phosphatase test and other methods are in general use Inspection of pasteurization equipment itself is now diligent, with a few known exceptions Automatic records of pasteurizing temperature are generally required. In spite of such precautions, bootlegging of raw milk or sale of improperly

pasteurized milk can and probably does go on in some communities, just as other health ordinances are violated.

However, that pasteurization of even Certified Milk is a proper added precaution against milk-borne *Brucella* infection is shown by such occurrences as the following:

Certified Milk in San Francisco Bay area was grossly infected in 1917.[illegible] *Brucella abortus* was reported in 10 of 230 samples of Certified Milk from the Detroit, Michigan, area in 1931.[illegible] The 10 positive samples were obtained from three of the five dairies involved. Hasley[illegible] cited Evan's report in 1915 of the isolation of *Brucella abortus* from 14 of 46 milk samples, in two certified dairies, ranging from 110 to 4300 per cc. of milk. Also cited was Carpenter and Boak's report in 1925 of infection in the milk from 6.06 per cent of 578 cows from three certified dairies.

Such reports were frequent prior to 1930 when requirements for *Brucella* control were introduced into Methods and Standards for the Production of Certified Milk. Since these methods were introduced reports of *Brucella* infection in Certified Milk have been few but they have not ceased.

Fitch and Bishop[illegible] in 1939 reported finding an agglutination titer of 1:100 in the whey of milk from a herd producing Certified Milk; guinea pig inoculation showed *Brucella abortus*. Another sample of the Certified Milk taken at a later date showed similar results.

A case of brucellosis in a woman occurring in October 1942 in which epidemiologic evidence indicated Certified Milk as the source was described by Perkins.[illegible] Eight of the 765 cows in the herd gave positive tests for Bang's disease in the same month. Brown pointed out that all of the 8 cows were in their dry period and had been negative at the time that they were removed from the milking herd. He thought that they might have become infected by a cow which aborted in the dry group while on pasture. There is no possibility of proving that these 8 cows were not shedding organisms in their milk or serving as sources of infection to other cows, not yet discovered to be infected, before their removal from the milking herd.

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Tiedeman[44] stated in 1946 that the Bureau of Milk Sanitation, New York State Department of Health, had not found a single reacting goat and that the smaller number of goats as compared with cows in New York State (10,000 to 1,400,000 in 1940) may account for the slower spread of goat infection. Tiedeman and Winters agreed that occasional importations of goats from the Southwest where goat infection is rife may materially change the situation at any time.

The supposed low incidence of infection in goats in some areas may be at least partially attributable to error in considering blood-agglutination reactions in low titer as insignificant. The actual incidence of goat infection in the United States is unknown. There were 8.5 per cent of reactors among 14,339 goats in 131 herds tested in Colorado in 1944.[61] Along the Mexican border the incidence is known to be much higher. In some Central and South American countries and along the Mediterranean, infection has been reported in 50 per cent of goats.

Data and opinions on this point are controversial. Stone[53] failed to find any definite evidence of infection in 419 goats other than agglutination reactions in titers of 1:50 in 20 animals, 3 "in a higher titer," and none as high as 1:100. No organisms or agglutinins were found in the milk, three of the goats with blood agglutinins in titers up to 1:50 were autopsied, with negative cultural findings. In spite of this negative evidence it would be advisable to forbid importation of goats showing agglutinins even in such low titers and to forbid sale of any raw milk from goats. (For further discussion see pp. 55, 56.)

The milk of infected ewes, mares, and asses also is known to be infectious for man.

Suis *Infection in Cattle*

Swine infection was found in 3 per cent of 1,547 hogs by the rapid agglutination method.[42] *Brucella suis* was isolated from 41 per cent of 34 reacting animals. Agglutinins are likely to be absent in even larger percentages of infected hogs than in infected cattle; the percentage of infected hogs must therefore be as-

Some outbreaks or sporadic cases of brucellosis undoubtedly are wrongly attributed to Certified Milk. Dooley[150] reported an epidemic among 263 persons using infected raw milk in a Connecticut boys' school in 1932 which he ascribed to "Certified Grade A Milk." There had been an epidemic of contagious abortion in the herd five years before. There was no evidence that this milk was produced under authority of the Certified Milk Commission. It seems likely that the use of the term "Certified Grade A Milk" was inadvertent and was intended only to mean that the herd was then "certified," as free of brucellosis (which it obviously was not). The term "accredited" would have been a better one.

That Certified Milk, raw, is a potential source of human brucellosis seems evident. (See pages 491–502.)

Cream is an even more likely source of infection than market milk or skim milk, since it furnishes a better medium for the growth of *Brucella*. Avoidance of milk as a beverage but use of whipped cream or cream in other beverages may be a frequent source of infection.

Milk-borne brucellosis caused by *Brucella abortus* is nearly always a sporadic occurrence whereas the *suis* strain is likely to cause multiple cases (p. 87) Jordan and his coworkers[386] stated that *Brucella suis* is more highly pathogenic than *Brucella abortus* and that the *suis* strain multiplies more rapidly in a milk medium under ordinary atmospheric conditions than does the *abortus* strain The pathogenicity of *Brucella melitensis* is also known to be great, with long periods of survival in dairy products such as cheese (p. 55).

Goat's Milk and Other Milk

Goat's milk is seldom pasteurized, constituting a major menace when produced from infected animals, because of the virulence of the *melitensis* strain and because cattle and hogs may become infected with this strain In the United States it is believed that goat infection is largely confined to the Southwest. Winter[712] stated that there is little natural infection in New York State

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sumed to be considerably higher than 3 per cent. The contact of infected hogs with cattle is known to lead to infection of milking herds and outbreaks of virulent infection from use of such milk, unpasteurized (p. 87). Instead of always aborting, sterility in the infected sow or production of large numbers of dead pigs is likely to occur.[473]

Transmission of *Brucella suis* infection from artificially infected hogs to cows running in the same pasture did not occur in an experiment reported by Elder.[192] In an editorial comment in *Veterinary Medicine* for July, 1947, doubt was cast on the whole question of natural transmission of *Brucella suis* infection to cattle. With one or two exceptions all attempts to transmit brucellosis naturally from swine to cattle by association have resulted in failure or questionable success, it was stated. However, 3 of the 8 cows in Elder's study aborted and several developed agglutinins in titers as high as 1·60 Although no organisms were recovered from the cattle or from aborted fetuses, Elder admitted the possibility that *Brucella suis* infection may have existed. This "negative" experimental evidence seems insufficient to offset the epidemiologic findings in milk-borne *Brucella suis* infections

Relationship Between Ingestion of Raw Milk and Intradermal Reaction

Of 1,122 students at Duke University, none of whom had any past history of acute or chronic illness suggesting brucellosis, positive skin tests were found in 127 (11 3 per cent).[475] When these were compared with 127 controls who had shown negative skin tests it was found that 114 (89 8 per cent) of the positive reactors had drunk raw milk in their homes, while only 46 (36.2 per cent) of the negative reactors gave a history of ingestion of raw milk.

Infectiousness of Strain 19

The infectiousness for human beings of strain 19 *Brucella abortus* organisms, when used for vaccination of calves or adult cattle, or when brought into accidental contact with human

beings, has been suggested. It is known that they may localize in the udder, without symptoms, and that they may be shed in the milk. Accidental infection of veterinarians and farmers handling this live vaccine has been reported.

OTHER DAIRY PRODUCTS

Dairy products, other than milk and cream—ice cream, cheese, butter, and buttermilk—are potentially infectious when made from raw milk. Cheese is generally accepted as an important source of infection in various parts of the world, especially in Mexico (p 55).

In 1928 Carpenter and Boak[115] inoculated two strains of *Brucella abortus* into cream stored at 8° C. and found that the organisms remained viable for eight days. Two other strains, one of human origin, infected guinea pigs for a period of ten days after being inoculated into cream The first two strains inoculated into butter stored at 8° C. remained viable and infected guinea pigs for periods of eighty-one and thirty-two days respectively. The other two strains were viable at the end of one hundred and forty-two days after being inoculated into butter, but not after one hundred and ninety-two days.

Butter, Buttermilk, Ice Cream

No statistics are available as to human infections ascribable to butter, ice cream, or buttermilk Since the organism has been demonstrated to survive for long periods of time in all of these media it must be assumed that such foods are infectious for man Although pasteurization of milk or cream for use in making ice cream and buttermilk is required in many communities and states, there is no legal provision requiring pasteurization of cream made into butter in many, including the City and State of New York

Cheese

Eighty-two samples of cheese were studied for evidence of infection by injection into guinea pigs[115] Seventy-two were im-

ported varieties, 30 from Italy, 14 from France, 13 from Switzerland, 6 from Holland, and the remainder from England, Germany, and North and South America. The majority of the samples were Swiss, Roquefort, Reggiano, Gorgonzola, and Edam None showed evidence of *Brucella* infection.

Subsequent observations have shown that cheese made from raw milk may harbor *Brucella* for one hundred days or more. *Brucella* were found viable after two months in Roquefort cheese, four months in refrigerated butter, and ten days in refrigerated milk.[648]

Death of a patient, apparently attributable to the ingestion of infected Italian cheese, was reported to the author by the attending physician, Dr. Louis Hauswirth[319] in 1940 (p 102).

Cheddar-type cheese, often called "bulk," "hard," "store," "American," or "country" cheese, is often made from unpasteurized milk, with no heat treatment in its manufacture. The so-called process cheeses are subjected to heat equivalent to pasteurization in the course of manufacture

Pasteurization of milk for cheesemaking apparently was first recommended by Sammis and Bruhn[596] in 1912. They pointed to the increased yield, avoidance of losses due to defective milk, the fixed time schedule for all operations, the more uniform quality and flavor, the lessened need for cold storage in curing, and the more sanitary product. Acceptance of the method has been slow, although it was soon found that pasteurization aided in the control of gas formation which is of special importance in warm climates.[57] The charge that pasteurization was being used to cover up use of inferior milk was met by showing that the quality of pasteurized milk cheese varied with the quality of the milk—that good cheese could not be made from milk of poor quality, whether or not pasteurized[544]

Expert cheesemakers state, no doubt correctly, that better cheese of some types, particularly Cheddar, can be made from raw rather than from pasteurized milk, because it ages more rapidly and develops better flavor Riggs considered this opinion to be probably the most potent factor in retarding the wide-

spread acceptance of pasteurization. Factors also mentioned were the tendency of cheesemakers to resist change and the almost prohibitive cost of pasteurizing equipment for the small manufacturer.

Tiedeman[643] stated in 1944 that it had long been recognized that cheese, particularly Cheddar, may serve as a medium for the transmission of pathogenic organisms. Of 31 outbreaks of infectious disease traced to cheese, 3 were severe outbreaks of typhoid fever attributed to Cheddar cheese; 1 occurred in Michigan in 1917, the second in Minnesota in 1925, and 1 in the St. Maris Valley, Quebec; one outbreak of paratyphoid B was attributed to Italian cheese. An outbreak of typhoid in 1941 was traced to contaminated cheese curd and fresh unpasteurized American cheese. There is evidence that other disease, especially scarlet fever, septic sore throat, and undulant fever, may be similarly transmitted. Only a few of the largest manufacturers make cheese from pasteurized milk, although good cheese can be made from pasteurized products, with the exception of one or two varieties which, for commercial reasons, must be aged In the past, it has been customary to age cheese for from three to six months. War shortage and a lack of a ceiling price differential for aged cheese appeared to have stimulated the practice of marketing unripened cheese, apparently resulting in the marked increase in outbreaks of cheese-borne disease.

Two varieties of cheese were studied to determine the occurrence and survival of *Brucella abortus*.[259] The findings were as follows. (1) Cheddar cheese was made from milk from a highly infected herd. The milk contained about 500 viable *Brucella abortus* organisms per ml This was inoculated with a freshly isolated culture of *Brucella abortus* so that it contained about 1000 organisms per ml. *Brucella abortus survived in the cheese for six months at 4 4° C*, as shown by guinea-pig inoculation. All the cheeses were negative for *Brucella* in one year (2) Milk was obtained from reacting cows purposely selected because of their elimination of large numbers of *Brucella abortus*, giving plate counts from 700 to 800 *Brucella abortus* per ml *When this*

milk was made into Cheddar cheese the organism remained viable for three months in all of the cheeses, had disappeared in some of the cheeses in six months, and was negative in all guinea-pig inoculations in all the cheeses within one year. (3) Tests were conducted on 10 vats of milk which were to be made into Limburger cheese and 15 vats which were to be made into Cheddar cheese, in New York State, in areas selected at random. Two of the vats of milk to be made into Limburger cheese were positive for *Brucella abortus* on guinea-pig inoculation; no Cheddar-cheese milk was positive. The Limburger curds made from the positive milks were negative and the cheese was negative when it was first tested after fifty-seven days of storage. (4) Tests were conducted on 34 vats of commercial Cheddar-cheese milk in New York State and in Wisconsin where brucellosis still existed in the milking herds. There were 9 positive milks and 8 positive curds. Seven cheeses made from known infected milk were free from viable *Brucella abortus* organisms on the first examination made after the cheeses had been stored for from forty-one to eighty-four days at 1.1 to 2.7° C. (5) Of a total of 59 vats of commercial cheese milk 11 were positive for *Brucella abortus.* Three vats of positive milk gave negative fresh curds. The Cheddar cheeses from the nonpositive milk were negative on first examination after storage from 1.1 to 2.7° C. for periods varying from forty-one to eighty-four days. No *Brucella abortus* organisms were recovered from any sample of commercial cheese. The authors considered that the experimental data on commercial cheese showed that an aging period of sixty days is reasonable assurance against presence of viable *Brucella abortus* organisms in Cheddar cheese.

The more rapid death of *Brucella abortus* in commercial cheese as compared with inoculated laboratory samples was attributed to the fact that the commercial cheese had a very much lower initial contamination. However, it must be pointed out that when the milk used for the production of cheese came from heavily infected animals (milk containing from 600 to 800 *Brucella abortus* organisms per ml.) the organism remained viable in all the Cheddar cheese for three months, "could not be demonstrated

in *some* cheeses in six months," and was negative in all cheeses in one year.

An exception is *Brucella melitensis* in goat's milk cheese,[259] which presents a special problem: Stiles [651] had reported the isolation of *Brucella melitensis* from 16 specimens of cheese, made entirely or largely from raw goat's milk, from herds known to be heavily infected. The estimated age of the cheese from which the organism was recovered varied from thirty-eight to one hundred days; in one specimen age was unknown, these cheeses were of the feta, yellow cream, and Romano variety, manufactured in Colorado.

A case of *Brucella melitensis* infection in which the cheese in question was reported to be made from raw cow's milk, without the addition of goat's milk, was cited by Stiles.[652] The cheese proved to be infectious for guinea pigs and ultimately *Brucella melitensis* was recovered Later it was discovered that this creamery purchased a 10-gallon can of goat's milk each week from a small goat herd nearby Infection was found in these animals. It must be stressed that it is not only goat's milk which may contain the *melitensis* strain, cows having been shown to be susceptible to and capable of shedding this virulent species

Tucker and his coworkers [675] added further evidence of the lack of safety of unpasteurized cheese, isolating *Salmonella typhimurium* from Colby cheese and reporting that this organism remained viable in the cheese for three hundred and two days, when held at 43–48° F They pointed to the experimental studies of Campbell and Gilman, showing that *Eberthella typhosa* and *Brucella abortus*, as well as other pathogenic organisms, could survive in cheese

In Mexico City use of cheese made from unpasteurized milk accounted for over 62 per cent of the infection (see p 82) Cow's milk and goat's milk is frequently mixed in making cheese in Mexico Only about 30 per cent of infection was attributed to milk and cream (12.7 per cent to raw cream, 10 per cent to raw milk of cows, and 7 2 per cent to raw milk of goats) It was suggested that this preponderance of cheese-borne infection was

due to (1) use of large quantities of cheese, (2) use of but little goat's milk as such, and (3) boiling of milk.

Breed[82] stated that Cheddar cheese of very satisfactory quality can be made from pasteurized milk, and that one of the larger manufacturers reported pasteurization of all milk to be made into Cheddar cheese. This was confirmed by Riggs.[573]

Such cheeses as Limburger, Muenster, Camembert, Brie, Edam, Gouda, and Swiss when imported into the United States must conform to the laws of the state in which they are sold. New York, California, Indiana, Illinois, and some other states require pasteurization of milk for cheesemaking or of the cheese itself, or a holding period of sixty days. Canada, where nearly all Cheddar cheese is made from raw milk, requires a holding period of ninety days Colorado, where goat's milk is often used in cheesemaking, requires a holding period of one hundred and twenty days for cheese made within its borders. *However, since the* melitensis *strain may be present in such cheeses and since even the* abortus *strain may survive more than sixty days, it is suggested that any cheese, foreign or domestic, be avoided unless it is made from pasteurized milk or is subjected to equivalent heat in its manufacture or is aged for six months or more.*

WATER

Water, except rarely, when grossly contaminated with *Brucella* organisms, seems to be an unlikely source of human infection. Contamination of water with the urine or discharges of milk of infected animals, was suspected as a source of human infection by Gershenfeld and Butts[254] but no proof was offered. Del Sel[173] considered water a likely source of infection, pointing to the occurrence of endemic brucellosis in a town in Argentina. the water supply of which was exposed to contamination by the feces of sheep and goats, as contrasted with a neighboring town with a well-protected water supply in which the disease was not endemic.

An accidentally contaminated water supply was suspected of being a means of transmission in a mid-Western university in

1938–1939. Between December 10, 1938, and February 10, 1939, a total of 45 cases of clinical *Brucella melitensis* infection occurred, with one death. Forty-one were students, 1 a laboratory stockroom attendant, 1 a plumber, and 1 a salesman. Forty-nine other persons were thought to have developed a subclinical infection *Brucella melitensis* was cultured from the blood of 36 of the clinical and 3 of the subclinical cases. No other species of *Brucella* were recovered Inadequate sterilization of infected labora- [illegible]

quate sterilization might have occurred at times, considered it unlikely that the water supply could have been contaminated They presented evidence for and against mass infection from a single source (e g. the occurrence of the majority of both the clinical and subclinical cases in three laboratory classes) and considered the possibility that the epidemic might have originated from carriers and have spread from one person to another as a result of being associated together for a period of time. They concluded that there was insufficient proof to explain how the epidemic originated

UNCOOKED OR INADEQUATELY COOKED MEAT

Uncooked meat as a potential source of infection when ingested by packing-house workers (many of whom taste "precooked" meat) was mentioned by Borts [71] The hazard to the general population from eating raw meat, such as chopped beef, must be considered relatively remote since cattle known to be infected are not slaughtered and sold for household use, and since the habit of consuming beef in the raw state is not common Danger from inadequately cooked commercially available meats in general also seems small since relatively low degrees of heat kill *Brucella* Lehr [432] considered home-made inadequately cooked summer sausage hazardous, however no outbreaks of brucellosis in families or other groups who have consumed parts of the same cuts of raw or poorly cooked meat have been reported.

DIRECT CONTACT

Hutchings[370] pointed out that there are marked differences in the infectiousness of beef and pork, based on the following observations: When the bovine type enters the body of a susceptible animal it circulates in the blood for a short period only, then localizing in the uterus or udder. The *suis* type circulates in the blood for a long period, often sixty to ninety days, and then may localize in any tissue. Since the uterus and udder are not used for food there is little danger to man from the consumption of beef from an animal infected with *Brucella abortus.* Edible portions of pork from an infected animal may endanger the butcher and the housewife who handle the meat, he stated. However, no one has done more than to theorize as to this mode of infection by handling meat in preparation for cooking. There are no reports of having cultured *Brucella* from edible parts of animals as sold in shops.

Occupational Factors

Veterinarians, farmers, dairymen, cow, sheep, goat and swine herders, butchers, stockyard and packing-house workers, and laboratory personnel are likely to contract clinical or subclinical infection with one or more of the three species of *Brucella* by direct contact in the course of their routine work. The annual infection rate of 271.5 per 100,000 for packing-house workers, of 250.0 per 100,000 for veterinarians, and of 43.0 per 100,000 for farm workers, as contrasted with rates of 3.3 for merchant-professional groups, 2.2 for farm wives, 1.4 for housewives, gives graphic evidence of the importance of direct contact with infected animals, their freshly slaughtered carcasses, and their products of conception. The fact that the exposure from direct contact often is overwhelming and likely to produce readily diagnosable acute illness, whereas chronic infection from other sources in the general population (housewives, merchant-professional group, etc.) is likely to go undiagnosed does not detract greatly from the significance of the findings in this study (Table III). It lent strong

TABLE III

BRUCELLOSIS OF MAN IN IOWA [a]

Based on 1338 case reports supplied by Iowa physicians, 1942-1945 (105 cases through 11/15/45)

Occupation or group	Area	Contact with hogs and cows		Users of unpast. milk		Total cases	Population in group	Annual number and rate	
		no.	%	no.	%			3 year av'ge 42-44	Annual rate per 100,000
Child (12 yrs & under)	Rural	10	50.0	20	100.0	20	916,708 [b]	8.0	0.9
Teen age	Rural	26	72.2	36	100.0	36	916,708	8.3	0.9
Farm wife (adult female)	Rural	50	60.0	92	100.0	92	916,708	20.0	2.2
Farm worker (adult male)	Rural	611	100.0	611	100.0	611	311,770 [c]	194.0	13.0 [f]
Child (12 yrs & under)	Urban	5	27.8	18	100.0	18	1,021,500 [d]	5.7	0.4
Teen age	Urban	6	31.6	16	84.2	19	1,021,500	4.0	0.3
Housewife (adult female)	Urban	3	3.2	77	81.9	94	1,021,500	22.0	1.1
Merchant professional	Urban	57	26.0	159	72.6	219	1,021,500	52.7	3.3
Packing-house worker	Urban	205	98.1	69	33.0	209	20,000 [e]	54.3	271.5 [f]
Veterinarian	Urban	11	100.0	8	72.7	11	800 [e]	2.0	250.0 [f]
TOTAL		909	71.7	1,115	83.3	1,338	2,598,208	311.0	12.3

[a] Iowa State Department of Health, Division of Preventable Diseases (C. F. Jordan, Director). [b] Farm population, Census 1940. [c] Male farm workers, Census 1940. [d] Urban and nonfarm population, Census 1940. [e] Estimated number. [e] Approximate number. [f] Specific rates per 100,000

support to the theory that direct contact is of far greater importance than ingestion of raw milk or dairy products *in certain occupational groups.* It must be emphasized that in the United States these occupations represent only about 10 per cent of the total population. Milk, cream, and dairy products, unpasteurized, still must be considered the major source of infection in the remainder of the population.

The Skin as a Portal of Entry

The normal skin of guinea pigs was shown to be more vulnerable as a portal of entry than the digestive tract;[203] epidemiological evidence exists that the same is true in man. The organisms gain entrance without causing local lesions; therefore the probable portal can be determined only by considering the types of exposure, the dosage, and the resistance to invasion of the different portals. It was felt that ingestion is not a satisfactory explanation for the natural and ready transmission of contagious abortion among animals and that more consideration should be given to the skin as a portal of entry. Guinea pigs exposed by bringing the organism in contact with shaved and abraded skin were 100 per cent infected, with both the *abortus* and *suis* strains. Guinea pigs whose skin was shaved but with no abrasions showed infection in 95 per cent with the *suis* strain and in 82 per cent with the *abortus* strain Guinea pigs in which hair was only clipped showed infection in 81 per cent with the *suis* strain and in 73 per cent with the *abortus* strain Guinea pigs fed the organisms by mouth showed infection in 17 per cent from the *suis* strain and 33 per cent from the *abortus* strain It was concluded that the proportion infected by feeding varied with the dose used, in all probability. Jordan's[39-] later observations strongly supported these views

Other Occupational Factors (Animals, Birds, and Insects)

The packing industry is reluctant to consider brucellosis as occupational and it is difficult to secure adequate and accurate clinical, epidemiologic, and serologic data relative to this disease

from such sources.[71] Of 24 cases of brucellosis observed by one worker, 23 were engaged in hazardous occupation; 17 of these were packing-house workers.[437] Nine of the 17 workers ate precooked meat products.

Contact infection possibly may occur even in persons whose occupations seemingly preclude this likelihood. Lamoreaux [424] stated that *Brucella suis* was isolated from the blood of a railway conductor who later recalled his casual contact with hogs as they were being unloaded.

In localities where milking of goats was done by men, men were commonly infected, and in places where the milkers were women, as in Corsica, most of the cases were among women.[135]

Horses may be a source of infection to man, directly or indirectly. Fitch and Dodge [220] discussed the spread of Bang's disease from horses to cattle. Carpenter and Boak [121] reported that 49 per cent of sera from 347 horses showed specific agglutinins in titers of from 1:25 to 1:100 or higher. In a group of mares which had been in contact with infected cattle, kept under observation for two years, some developed high titers and became temporarily sterile. Two of the 5 with fistulous withers showed blood agglutinins in titers of 1.100 and 1:200, one of them yielding a bovine strain of *Brucella* from the purulent exudate Two children having contact with this horse developed brucellosis

Way [696] repeatedly noted failure of efforts to clean up infection in cattle herds until an infected horse was discovered and removed from the farm Fistulous withers and poll evil from which *Brucella abortus* could be recovered, or high blood-agglutination reactions were noted Stone [653] also mentioned suppurative lesions in horses as due to *Brucella abortus* He found a higher percentage of infection in horses on farms, where there was contact with cattle, than in urban horses. The infection rate varied from 31 to 50 per cent

Animals other than the cow, sheep, horse, goat, and hog are less likely sources of human infection by direct contact but may be reservoirs of infection of varying degrees of importance. Birds and insects must also be considered in this possible category. It is

likely that there is some reservoir of infection, other than in the domestic animals, which perpetuates the infection in domestic stock.[388]

Mules may be infected, 37 positive blood-agglutination reactions having been found on the island of Malta.[394] They were considered to be infectious for man.

Cats have been found to be infected.[625] Transmission to man is unlikely but the feces may contain viable organisms.[284]

Dogs have been cited as a possible source of human infection.[169, 501] Muhlenbeck's patient had an attack of acute brucellosis following the bite of a cow hound which guarded a herd of infected cattle. The blood of both patient and dog showed a positive agglutination test in a titer of 1 400. The organism was isolated from the kidneys of the dog. However, the patient as well as his family had been drinking the unpasteurized milk from the infected herd which seems a more likely source of his illness.

Feldman, Mann, and Olson [232] reported blood-agglutination reaction in titers of 1 100 or higher in 10 4 per cent of 500 dogs living in a rural environment. In the Congo, Van Saceghem [881] reported that when abortion was of frequent occurrence among cattle, it likewise occurred among dogs He considered the dog a possible agent in transmission of infection

Sheep have been considered a source of human infection with the *melitensis* strain through direct contact or ingestion of ewe's milk.

Asses may be a direct source of human infection, or through their milk

Bison are naturally infected, reports of 44 to 74 per cent of reactors among various groups of bulls, steers, and cows having been cited [149, 388, 594, 877] They are possible sources of infection for cattle and thence for man

Elk show a lesser percentage of infection [144, 877] but may be a menace to domestic animals

Moose, so far as has been determined, are not infected in large numbers.

Deer (whitetail) in Minnesota, Michigan, and Pennsylvania showed no evidence of infection [388]

Foxes were reported [470] as aborting when they contracted the infection They would therefore also be suspected of transmitting the infection to other animals

Rats may become infected naturally by ingestion of contaminated food and may pass the infection to other rats. The urine of infected rats may contain the organism and thus be a source of infection of other animals and man.

Guinea pigs are known to be extremely susceptible to artificial infection but have not been reported as naturally infected

Chickens are susceptible to naturally occurring infection [182, 217, 358] Both *suis* and *abortus* infections have been found in fowl in the United States. Dubois [182] reported a highly fatal epidemic among chickens on a farm in France where there also was infection in sheep

Turkeys, pigeons, ducks, pheasants, and *geese* were considered by Emmet to be susceptible to infection but with no proved evidence of infectiousness to each other or to cattle [398]

English sparrows have been considered to be susceptible to naturally occurring infection but not necessarily able to transmit the disease.

Flies of several species including *Musca domestica* L, *Muscina stabulans* F, *Stomoxys calcitrans* L, *Calliphora,* and *Lucilia* may excrete *Brucella* in intestinal droppings for four days or longer [208, 593] They must be considered a possible means of transmission from animal to animal and from animal to man, although attempts failed to transmit infection to monkeys through exposure to flies

Cockroaches (the common species, *Periplaneta Americana*) are not important conveyors of *Brucella,* excreting *Brucella abortus* which does not remain alive for more than twenty-four hours.[593]

Mosquitoes (*Stegomyia fasciata* and *Acartomyia Zammitii*) excreted *Brucella melitensis* forty-eight hours after feeding on the blood of infected guinea pigs [208] They failed to transmit infection to monkeys

Laboratory Infections

No complete statistics as to laboratory infections in the United States have been published.[464] There can be no doubt that these infections occur frequently.

Records of 74 instances of *Brucella* infection of laboratory employees in the United States between 1922 and 1939 were compiled,[464] distributed among 7 centers of *Brucella* research (66 cases) and 7 other laboratories doing less work with live organisms (8 cases). Forty-four were bacteriologists handling cultures and specimens, 6 were animal caretakers, 4 were pathologists, 3 cleaned glassware, 3 were janitors, 2 were parasitologists, 2 were laboratory aids, 2 cared for hogs. One each were engaged in preparation of antigen and vaccine, handling hog tissue, breeding cattle, interning in a *Brucella* laboratory, research work involving autopsies on guinea pigs, handling infected goat's milk in laboratory experiments, visiting a laboratory, or carpentry in a goat shed All three strains of *Brucella* were involved although the great majority were due to *Brucella melitensis*. *Brucella suis* appeared to be equally infectious under similar circumstances and *Brucella abortus* to be less so.

The same authors considered that the handling of *Brucella abortus* in cultures and tissues is attended by less risk than *suis* or *melitensis*. They pointed to the possibility of dust in animal pens or thrown off by centrifuges in laboratories as a source of infection. Unpublished data of Fleischner and Meyer were quoted as to the infection of monkeys by *Brucella melitensis* in dust

Acute brucellosis in 17 laboratory workers engaged in investigative work with strains of *Brucella suis* and *Brucella melitensis* in an Army Station Hospital has been reported.[315] *Brucella suis* was isolated from the blood in 8 cases and *Brucella melitensis* in 7 cases.

It may not be possible to distinguish between laboratory infection and that of other origin, unless in epidemic proportions

Veterinarians

In 1931 Jordan[381] stated that "it is not improbable that veterinarians through repeated exposure in their contact with cattle acquire a degree of immunity." Kristensen and Holm[417] reported a series of 500 cases of undulant fever in Denmark without one occurring in veterinarians. Huddleson and Johnson[360] had elicited a history "characteristic" of undulant fever in only 3 veterinarians of a group of 49 examined. Jordan found a history suggestive of undulant fever in only 3 of 120 veterinarians in Iowa. Not mentioned were the possible chronic illnesses, of mild or severe degree, that might have been caused by *Brucella* infection.

Meyer and Eddie[434] stated that veterinarians are not very susceptible to clinical infection with the *abortus* strain because of immunization through continuous exposure to mild infection. Huddleson[351] observed that veterinarians who are engaged in cattle practice come in contact with *Brucella* to a greater extent than any other single group of people, and that a considerable percentage have *Brucella* agglutinins in their blood and give a positive intradermal test, while very few give a history of having a clinical course of the disease.

These observations are not borne out by the author's experience. Clinical brucellosis in veterinarians presumably exposed only to infection in cows has been observed in 9 veterinarians and the reports of many others reviewed. The illnesses varied from mild ambulatory cases to severe acute febrile illnesses. In fact, no veterinarian engaged in cattle practice for a period of years escaped brucellosis in some form. Diagnostic criteria to distinguish latent from clinical infection are not uniform.

In 1946 Jordan[382] reported a morbidity rate for veterinarians of 250.0 annually per 100,000 in Iowa from 1942 to 1945. The only higher rate was that of 271.5 among packing-house workers. The rate for farm workers was 43.0 and for urban merchant and professional groups 3.3 (Table III, p. 59). He reported 11 clinical cases of brucellosis among veterinarians. It is apparent that brucellosis must be considered a common occupational disease in

veterinarians, if acute febrile illness is not considered the only criterion of active *Brucella* infection.

Other Possible Modes of Infection

Manure as a source of infection was considered by Taylor and his coworkers,[601] stating that circumstantial evidence points to it as being a source of danger. The possibility seems remote except perhaps to the farmer or stockyard worker who is in direct contact with fresh manure

Dust as a source of human infection has been suggested.[343, 444] Dust in animal pens or thrown off by centrifuges in laboratories were the sources suspected.

INCIDENCE

Table IV gives an incomplete idea of the incidence of human brucellosis in the United States since necessarily it is based on reported cases only. It is impossible to do more than guess at the additional cases not reported, because they are undiagnosed or because chronic infections commonly are not reported when diagnosed At least 90 per cent of cases are chronic infections If the reported cases represent only or largely acute febrile illnesses, it is reasonable to assume that ten times the number of reported cases more nearly expresses the true incidence of the disease. Since the infection may be of indefinite duration, cases are cumulative. With 4,000 to 5,000 cases reported annually, it is probable that 40,000 to 50,000 or more infections, of varying degrees of severity, occur annually In a ten-year period several hundred thousand cases, clinical or subclinical, may be expected to have accumulated.

Reported cases in other countries of the world are shown in Table V They are necessarily incomplete. The tremendous discrepancy between various countries of similar population, geographical location, and industry can only be explained by lack of recognition of the disease or lack of reporting (Similar discrepancies are noted among the states of the United States.) The very

few human infections reported in Turkey is in sharp contrast with the high animal infection rate in that country (p. 75). The extremely high morbidity rate in Italy is noteworthy (Table V).

INCIDENCE OF SUBCLINICAL INFECTION

The incidence of subclinical, and therefore of potentially active clinical infection, is impossible to determine An important percentage of cases cannot fail to be overlooked unless impracticably meticulous clinical and laboratory studies are used in surveys. Even the combination of blood-agglutination reaction, opsonocytophagic test, skin test, and culture will fail to uncover the infection in many patients The usual method of performing the blood-agglutination and/or intradermal test will fail to disclose a larger percentage

Agglutinins may be found in the blood of apparently well persons in the course of epidemiologic surveys They must be considered potentially ill. Hardy and his associates [295] found agglutinins in a titer of 1·2560 in the blood of a 21-year-old packing-house worker who had no symptoms of illness. One month later he complained of profound weakness which was followed by acute illness and death within three months of myocardial failure. Blood culture yielded *Brucella suis.*

Mild or subclinical infection with the *abortus* strain undoubtedly is more common than severe infections [46, 180, 376, 703] Most of these patients are ambulatory and working in spite of low-grade fever, fatigue, arthritis, or various other symptoms. Jordan [381] reported 43 per cent of persons drinking milk from an infected herd to have agglutinins in a titer of 1·10 or higher, in one man, who was symptomless, *Brucella abortus* was cultured from the blood Among 197 apparently well persons 6 6 per cent had agglutinins in a titer of 1 20 or higher and 20.8 per cent showed positive skin reactions [180] Among 100 patients served with raw milk from an infected herd in a hospital for epileptics, 41 per cent had agglutinins in titers of 1 10 or higher and 45 per cent had positive intradermal reactions, of these, 22 per cent showed physi-

TABLE IV

REPORTED CASES OF BRUCELLOSIS IN THE UNITED STATES *

Division and state	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
NEW ENG.																					
Maine		9	2	10	5	15	25	24	20	13	28	26	28	28	33	25	48	37	41	37	33
New Hampshire			1	2	1	4	9	9	1		4	6	4	2	16	31	9	1	9	35	24
Vermont		2	2	19	17	13	14	25	27	24	41	42	30	41	61	59	47	88	70	82	137
Massachusetts			7	12	15	15	11	15	42	55	43	37	40	52	86	35	43	47	50	52	76
Rhode Island			3	2	0		11	9	15	12	16	9	18	12	11	9	8	16	21	16	18
Connecticut		13	12	21	20	34	36	55	59	99	74	96	71	91	123	72	74	61	125	104	181
MID ATL.																					
New York	21	65	104	165	171	224	253	301	230	212	190	253	253	255	288	239	286	245	279	308	262
New Jersey	2	1	13	17	19	36	28	27	34	64	67	52	62	76	61	47	71	63	70	50	43
Pennsylvania	2	22	25	33	53	47	54	80	68	86	91	109	121	108	82	74	94	87	127	143	98
E. N. CEN.																					
Ohio	1	41	78	129	115	88	78	77	69	79	66	91	91	112	116	77	100	94	79	128	90
Indiana	1	40	13	31	27	50	15	34	15	15	20	52	58	57	24	31	61	81	58	151	115
Illinois	5	25	40	63	124	75	93	101	144	84	107	212	233	155	217	265	307	326	325	178	555
Michigan	26	38	4	15	19	45	81	102	73	89	78	140	252	133	149	121	109	96	230	135	304
Wisconsin	1	9	12	82	71	27	104	86	75	106	94	79	102	114	130	158	178	224	283	384	490
W. N. CEN.																					
Minnesota	8	14	15	65	72	65	80	104	115	84	89	87	93	119	160	260	310	326	312	420	391
Iowa	14	129	172	145	48	88	151	177	112	113	137	124	388	230	354	393	418	295	182	648	902
Missouri		31	50	137	162	179	79	53	69	36	34	32	26	25	832	18	49	30	55	53	141
North Dakota		5	5	10	12	1	4	.	2	2	1	8	3	8	7	12	20	3	13	13	3
South Dakota	1	1		4	6	3	3	6	3	4	2	3	.	1	9	7	25	25	44	67	80
Nebraska		9	8	8	5	2	3	4	2	1	2	.	2	17	5	53	5	1	1	35	93
Kansas	3	14	85	100	61	79	86	99	98	97	82	133	109	170	114	93	179	175	209	281	151
S. ATL.																					
Delaware		3	5	7	2	2	6	10	9	.	..	6	3	5	1		3	1	1	3	7
Maryland	2	11	18	32	17	19	39	19	37	41	44	61	59	28	34	20	19	32	13	70	33

Dist of Col	2	2	1	1	3		1	1	2	1	1	4	6	5	3	4	1	3	2	.	
Virginia	2	6	4	25	20	37	14	34	39	33	37	50	22	23	16	34	37	35	33	70	70
West Virginia				1	5	1	2	2	3		7	8	9	5	7	3	3	6	12	11	15
North Carolina		3		2		4	15	19	31	23	26	29	25	11	12	9	9	12	15	9	21
South Carolina		2	11	7	3	3	10	18	11	9	14	28	32	33	11	8	14	20	25	40	49
Georgia		39	14	28	38	35	30	63	62	60	58	82	121	123	123	129	98	168	165	169	148
Florida		1	8	4	3	2	6	9	68	16	37	42	53	46	21	37	36	33	27	81	67
E S Cen																					
Kentucky		30	19	8	20	7	8	8	36	46	30	44	19	22	20	18	19	40	20	23	17
Tennessee		80	5	11	7		12	4	9	26	10	24	22	39	27	13	43	53	45	70	88
Alabama			17	23	20	17	12	45	54	43	48	59	59	70	45	70	69	91	104	102	124
Mississippi			3	7	3	11	13	3	14	21	23	32	25	30	24	28	12	50	100	133	86
W S Cen																					
Arkansas			2		12	12	10	11	16	35	30	23	36	21	22	22	13	38	51	75	48
Louisiana		1	17	20	59	35	24	54	49	37	56	60	57	73	64	56	58	37	77	66	44
Oklahoma			4	2	13	5	15	4	10	96	505	1589	372	112	117	69	30	16	37	36	88
Texas			3	3	11	93	43	21	40	43	198	239	327	354	330	231	339	470	616	750	460
Mountain																					
Montana		2	3	4	4	11	17	15	11	4	9	7	3	7	11	5	11	10	9	12	6
Idaho			1	2	23		18	2		4	14	6	16	7	10	2	1	2	24	23	31
Wyoming			2	2	1		1	2	1	2	1	4	13	19	13	9	7	6	4	4	1
Colorado		1	5	2	7	6	2	7	1	3	5	16	37	50	30	12	13	48	61	54	183
New Mexico	2	1	2	2	5	3	7	5	12	11	8	17	13	31	0	4	15	11	6	9	3
Arizona	5	8	13	16	12	11	27	18	4	35		31	39	29	21	18	18	27	13	34	21
Utah			2		11		9	8	5	3	5	12	28	14	11	7	15	19	99	35	89
Nevada		2	3		0	1	1		1	2	7	2	1	2	2	13	8	4	3	7	1
Pacific																					
Washington		1	22	33	34	18	24	25	35	34	26	40	25	28	42	73	43	56	54	54	65
Oregon		12	19	26	24	22	25	35	10	21	10	22	20	7	23	18	32	277	153	31	19
California	14	11	72	115	103	107	132	157	150	172	188	243	279	280	318	222	243	335	270	295	280
Total	112	669	975	1435	1578	1502	1788	2017	2008	2095	2075	4379	3501	3310	3184	3228	3734	4286	4959	5887	6147

* U S Public Health Service *The Notifiable Diseases, Reported Incidence of Certain Communicable Diseases by States.*

TABLE V

CASES OF BRUCELLOSIS REPORTED IN VARIOUS COUNTRIES *

Country	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
AFRICA												
Algeria	82	27	47	44		33	26	5	30	29	39	27
Angola	2	1	1									
Belgian Congo	1	1	0									
Gold Coast		6	8									
Egypt	13	19	20	38	27	20	0	6	20	15		
Kenya	9	12	21		25	121	18	10	6	24		
French Morocco	4	4	8	5	1	11	18	5	2	4	12	3
Uganda	7	0	0									
Southern Rhodesia	0	0	1									
Anglo-Egyptian Sudan	58	43	28	29	43	31	17		66	70		
Tripolitania										5	62	20
Tanganyika	8	9	3									
Tunis	16	23	7	4	1	6	11	3	3	2	1	2
Union of South Africa	15	4	8	9	14	14	10	21	20	4	6	
AMERICA												
Alaska	0	0	1									
Bermuda	0	1	2	3	13	17	3	1	1			
Canada	179	179	179		148	169	152	189	208	289	450	389
Chile	2	8	7	9	31	17	9	47	38			
Cuba	0	2	0									
Mexico	202	419	964	624	1,048	1,500	1,268	1,174	1,297	1,438	1,657	1,993
Peru	138			140	108	130	393	667	866	501	363	
Puerto Rico	0	0	1									
United States	2,095	2,673	4,379	3,501	3,310	3,484	3,228	3,771	4,130	5,049	5,687	6,124
ASIA												
Iraq												
Palestine	7	7	18	17	40	2	11	8	2	26	19	10
Trans-Jordan	1	1	1		20	5	10	32	11	6		
EUROPE												
Germany "Altreich"	15		19	276	218	189	178	122				
U. S. Zone										12	56	32

British Zone							..			.	73	63
French Zone									.		0	0
England and Wales				6	4	7	6	1	7	9		
Scotland	10	27	73								137	
Austria	56	61	12		40	30	17	37	.	7	29	23
Belgium					17	11	7	10	8	3	5	6
Denmark	607	570	585	523	558	408	345	327	262	284	201	279
Estonia	1							.			.	...
Finland	26	14	28	0	137	22	2	2	3	1		.
France	130	484	553	441	177	904	912	1,140	905	1,310	1,210	1,024
Gibraltar	1	0	0									
Greece	23	54	69	106	34	12	31	26	37	71	115	71
Hungary	0	1	0					..				
Ireland	0	0	3	3	0	1	3	0	1	0	3	5
Italy	3,116	3,948	4,015	4,627	4,615	4,173	4,553		5,696	6,332	7,123	8,272
Latvia	1	3	2							..		..
Malta and Gozo	873	1,034	985	873	950	619	450	534	173	1,024	2,410	1,458
Norway	0	10	24	5	0	0	3	2	3	1	0	3
Netherlands	27	27	34	29	24	18	41	22	6	0	7	8
Poland	13	13	16									20
Sweden	191	184	167	114	111	71	51	47	40	14	15	35
Switzerland	79	157	152	121	120	129	119	152	141	207	147	150
Spain					6,370	6,419	5,404	1,787	3,955	5,132	4,154	4,861
Turkey	6	14	15	0	1	0	0	0	0	0	0	1
OCEANIA												
Australia		4	5	12	0	4	7	9	16	14	15	20
Fiji	0	1	0								..	.
Hawaii	1	1	3	1	2	0	10	1	9	7	4	2
New Zealand	15	26	21	26	22	21	18	23	37	25	26	32
Maoris				1	2	1	3	2	2	0	1	..
YEARLY TOTALS ALL COUNTRIES REPORTING	8,409	10,070	13,113	11,503	18,244	18,070	17,528	9,956	18,310	21,089	23,960	24,970

* Compiled from data supplied by, United Nations, World Health Organization, Interim Commission, Division of Epidemiology and Public Health Statistics, through the courtesy of Dr. M Cakrtova, Medical Officer (based on incomplete statistics).

The ratio of actual to reported cases may be assumed to be at least 10:1. Note that no reports from Russia or Eastern European countries are available

cal evidences or temperature elevations indicating mild ambulatory active illness.[376]

The importance of this type of mild or subclinical illness is not adequately appreciated.

STATISTICAL SURVEYS

Various surveys of inmates of general hospitals, almshouses, and hospitals for mental disease and among school children have been reported. They roughly reflect conditions existing locally but are not truly representative samples on which to base accurate statistical conclusions. A survey of rural and urban population groups from various parts of the United States is needed to give a true picture. Such a survey would have to include careful clinical as well as complete laboratory study of each individual since none of the standard tests or even the combination of all are sufficiently informative to detect all infected persons.

The incidence of infection in purely urban populations has received little attention It is assumed that in cities where only pasteurized milk and cream have been used over a number of years the incidence must be very low. Ingestion of raw milk during vacations spent in the country, use of raw milk or cream in the remote past, unwitting ingestion of butter, cheese, and other dairy products made from raw milk or cream, and possible direct contact with infected animals are readily forgotten.

Evidence of infection in 10.3 per cent of 8,124 persons in hospitals (general and mental institutions) in Michigan in 1937 has been reported.[267] Later it was estimated that about 10 per cent of the population of the United States had become infected and that about 1 per cent of that number were actively and clinically ill with the disease The accuracy of this estimate can neither be affirmed nor denied.

Angle and his associates [23] found 9 per cent of positive reactors to the skin test in 7,122 school children, using Brucellergen as the skin-testing antigen.

Dustin and Weyler [156] studied 4,000 individuals in the State of Rhode Island over a period of four and a half years prior to 1940.

They were private patients, groups from outpatient departments, medical wards, almshouses, and patients in a hospital for chronic mental disease. They found clinical and laboratory evidence of chronic brucellosis in 441 or 11.0 per cent.

The experience of Lehr [432] in investigating the incidence of brucellosis in one county in Illinois suggests that similar conditions exist elsewhere The number of cases reported to the state from that area had been 1 in 1940, 2 in 1941, and 3 in 1942 Disbelieving these statistics because it was known that unpasteurized milk and butter from infected dairy herds was being sold, he attempted to uncover additional cases. He learned that two physicians in that area had diagnosed approximately 100 cases of brucellosis within the past two and a half years. Investigation revealed that most of the patients had seen other physicians without obtaining relief from their symptoms and had ultimately reached the two physicians mentioned. An epidemiologic investigation of 24 cases was made Eleven gave histories of drinking milk from infected cows. All gave histories of using unpasteurized dairy products or home-killed uninspected summer sausage. Only 10 per cent of the herds in the region had been tested but reactors had been found in 50 per cent of them

Although the morbidity rate is recognized to be much higher than reports indicate, comparative rates between various states or groups of states are significant Jordan and Borts [385] pointed out that North Carolina, the only state accredited in measures for eradication of brucellosis in dairy cattle, had the lowest rate among human beings for the twelve-year period from 1930 to 1941—0.4 per 100,000. Rates in other states varied from 0 98 to 3 34 per 100,000 Surveys indicated that the ratio of latent or subclinical to clinical cases may be 8 1 or higher.

It will be noted from Table IV that there was a steady increase in the number of reported cases of brucellosis from 1927 through 1938, rising from 112 to 4,379 The marked difference between the 2,675 cases reported in 1937 and the 4,379 cases reported in 1938 was because of the unprecedented number of 1,589 cases reported from Oklahoma in the year 1938, apparently the result

of special investigative work. From 1939 to 1943 inclusive there was no apparent increase in the number of reported cases. Since 1944 there has been a steady increase each year with a total of 6,147 in 1947; the significance of this steady increase is not yet apparent, but may be due to an increased awareness on the part of physicians. It might be expected that the various campaigns of eradication of *Brucella* infection in cattle, through slaughter, combined with widespread use of immunization of calves, would have been reflected in a lowered incidence of human infection. Such an actual reduction in human infection may be in progress but not reflected in the numbers of reported cases.

Accurate statistics were not compiled by the armed services in the recent war. Routine laboratory tests for brucellosis were not employed. Brucellosis was considered a cause for rejection when a definite history of active infection was given.

During four and a half years of naval service 26 cases of brucellosis were diagnosed by the author in the course of routine duties Some had been referred for an opinion as to diagnosis or treatment and some were diagnosed after suspicion of brucellosis had been aroused by suggestive symptomatology and confirmed by laboratory data It is certain that many cases occurred and were not diagnosed or were diagnosed subsequent to the war when more careful study was possible Many of these patients now are being seen in their veteran status or as inmates of Navy and Army hospitals.

The known incidence of brucellosis in the Navy and Marine Corps and the number discharged from the service with the established diagnosis of brucellosis for the years 1940 through 1944 is shown in Table VI

In March, 1946, it was stated by an official[703] of a large dairy corporation that not a single case of milk-borne disease had occurred among the 10,000,000 men trained for World War II, although a half-pint of milk per day was available for each man, some of which was raw milk. He was quoting figures derived from a seemingly unimpeachable source There was no intent to excuse the use of unpasteurized milk Indeed he remarked that even

TABLE VI

INCIDENCE OF BRUCELLOSIS IN THE NAVY AND MARINE CORPS *

Year	*Incidence*	*Rate per 1000 Average Strength*	*Invalidings from the Service*
1940	2	0 01	0
1941	13	0 04	3
1942	19	0 02	5
1943	61	0 03	14
1944	92	0 03	20

* Published through the courtesy of the Bureau of Medicine and Surgery, United States Navy

Certified Milk was considered all the more safe since its pasteurization had been initiated He intended only to point to the remarkably good record for milk in general in the war. He did not know that 180 men already had been invalided from the Army because of brucellosis, that the admission rate was about 0 04 per thousand mean strength per year, nor that the Navy had invalided a small but steadily increasing number from the service each year from 1941 through 1944 However, there is no way to distinguish infection contracted from milk during service in the armed forces from infection incurred from milk or by direct contact prior to service

GEOGRAPHIC DISTRIBUTION

Incidence and geographic distribution in man roughly parallel infection in cattle, sheep, goats, and swine, and to a lesser degree in other animals, throughout the world [43, 57, 369, 481] but accurate statistics are not available. Individual studies have shown extremely high incidence in some areas There were 56 52 per cent of reactors in cities and 77 90 per cent in rural regions among 1,237 persons tested, in and near Cordoba, Argentina [151] In Turkey, of 1,154 specimens of human blood, agglutination reactions occurred in 5 9 per cent, of 759 samples of horse serum, 40 per cent showed agglutinins, 62 5 per cent of mules, 31 1 per cent of beef cattle, 61 per cent of milch cows, 41 9 per cent of buffalo,

13.3 per cent of sheep, and 50 per cent of goats showed evidence of infection (*Veterinary Medicine*, July, 1947).

SIGNIFICANCE AND DISTRIBUTION OF THE THREE SPECIES OF BRUCELLA

The incidence of infection ascribable to each of the three strains, in man and animals, shows a wide variation. The relatively infrequent isolation of the organism, and the difficulty in assigning each infection to a proved origin, contribute to this situation. A given infection cannot be ascribed to the *abortus* strain simply because its probable origin is the cow; the cow is susceptible to and may transmit *melitensis* and *suis* strains.

In the Eastern United States, with its large milk-producing cattle population and relatively few hogs, *abortus* infections predominate in animals and man. In 1933, 113 of 117 strains (96 5 per cent) isolated from milk samples in New York State were *abortus* strains, the other 4 *suis*.[260]

Possibly indicative of the unsuspected existence of *melitensis* strains in cattle as well as goats is the following train of events which first came to light in 1947. About 1932 a farmer living in Essex County, New York, purchased 3 goats from another farmer in a neighboring township. Two of the goats aborted. Soon thereafter abortion first appeared in the cattle, previously free of apparent infection. Cows on neighboring farms, also previously free of infection, began to abort The wife of a neighboring farmer aborted during three successive pregnancies (p 120). The strain of *Brucella* isolated from her uterine discharge following the third abortion was only identifiable by the Division of Laboratories and Research of the New York State Department of Health as "of the *abortus-melitensis* group" It is quite possible that much more *melitensis* infection exists than is suspected in New York and other Eastern and Northeastern states. Culture of blood and milk of cows and goats rarely is carried out.

Brucella melitensis has been isolated from cow's milk in three widely separated towns in New York State[61] In two of the herds there was possible contact with goats.

Hardy and his associates [295] reported isolation of *Brucella* from the blood of 48 of 375 patients studied in Iowa. In one case both the *abortus* and the *suis* variety were isolated from the same blood specimen, giving a total of 49 strains, 35 were *suis* and 14 *abortus*. (A second instance of human infection with two strains of *Brucella*—this time *melitensis* and *suis*—was reported by Hardy, Jordan, and Borts [294] in 1936.)

Evans,[202] in 1937, pointing to the reports of *Brucella melitensis* infection in cattle in various parts of the United States, said

> On account of the much higher virulence of the *melitensis* variety for man, we can expect that whenever it infects cattle in any community in this country, our experience will be the same as that in the east of France—the proportion of human infections with the *melitensis* variety to infections with the *abortus* variety will be far greater than the proportion between the two varieties occurring in cattle As in Argentina, we in this country may also expect a greater proportion of severe cases in regions where *Brucella melitensis* exists.

Greater prevalence of *suis* infections in the Eastern United States also may be expected An example is that of a 42-year-old farmer from southern Maryland discussed on page 441. There was no history of abortion in his cattle at any time throughout his lifetime on the farm However, one sow had lost two litters about midway in its gestation period *Brucella suis* was isolated from the patient's blood

The hazard of exposure to the porcine or caprine strain is much greater than like exposure to the bovine strain, both in degree of infectiousness and in severity of the resulting illness Hardy, Jordan, and Borts [294] pointed to the very high attack rate of 7 7 per cent reported by Beattie and Rice [46] and of 4 8 per cent reported by Horning,[342] due to *Brucella suis*, as compared with that of 0 02 per cent among users of raw milk from dairy herds infected with the bovine strain Attack-rate statistics may be rendered inaccurate because *abortus* infections, being milder and rarely occurring in epidemic form, are more difficult of diagnosis and classification

In Iowa, of 127 strains isolated from man, 88 (69 3 per cent)

were *Brucella suis*, 38 (29 8 per cent) were *abortus*, and 1 (0 8 per cent) was *melitensis*.[394] (From this latter patient both the *melitensis* and *abortus* strain was isolated.) These findings roughly indicated the prevalence of *suis* strain infections in that hog-raising state. Many of these *suis* infections were the result of direct contact in the meat-packing industry. Some disproportion may be reflected in that *Brucella suis* is so much more readily recoverable from human blood or other source than is the *abortus* strain. The authors drew the following conclusions:

> The admittedly incomplete evidence derived from animal and human studies seems to indicate that in the New England, Middle Atlantic, East, North, Central, South Atlantic, and Mountain states a rather uniformly distributed bovine infection is largely responsible for undulant fever. The known case rates in these areas are quite similar. In the West Northcentral states approximately as many infections are derived from hogs, thus giving a total rate twice that of the aforementioned areas The low rates of the Southcentral states may be dependent on less adequate recognition and reporting or on rather widely differing socio-economic and racial factors The slightly higher than average rate in the Pacific states evidently reflects the keen interest in the disease on the part of workers in California, and also the known occurrence of the caprine infection in certain parts of this state

Cases per 100,000 population in states with the highest incidence were listed, giving three-year averages, as follows

Iowa	5 9	Maine	2 8
Vermont	5 5	Montana	2 7
Missouri	4 6	California	2 4
Kansas	4 3	Maryland	2 4
Arizona	4 2	New York	2 2
Delaware	3 5	Georgia	2 0
Minnesota	3 4	Louisiana	2 0
Connecticut	3 0	Wisconsin	2 0

Endemic occurrence of *Brucella melitensis* in Iowa was noted in 1945 [384] Twenty cases of human infection had been discovered within a two-year period Of 26 strains of *Brucella melitensis*

isolated, all but one had come to light since December, 1943. The solitary strain of *Brucella melitensis* which had been isolated in 1930 was from a patient who apparently had acquired his infection in Mexico previous to arrival in the United States. The first local cases were discovered in 1943 in 2 packing-house workers Fourteen additional *melitensis* strains were cultured from the blood of farmers and packing-house employees in 1944 and 9 more were discovered in the first half of 1945 Ten of the patients were packing-house employees, the remaining 10 farm workers, farm residents, or visitors. All except one had had contact with domestic animals. In the one in whom there had been no such contact there was possibly indirect contact incurred while painting a hog house. None had had contact with goats Only 7 had had contact with sheep and 5 of these had had direct contact with hogs, 3 with cows In the group of 10 packing-house employees, history of infection in animals was undetermined Among the 10 persons in whom infection apparently was acquired on farms, there was no history of abortion in sheep, however, on 5 of those farms sows had lost pigs and on a sixth farm 8 or 9 sows had recently reacted positively to the agglutination test It seems probable that *Brucella melitensis* has been introduced into Iowa during the past decade via sheep imported from Western and Southwestern sections of the United States

Table VII summarizes the origin of 463 strains of *Brucella* isolated in the Iowa State Hygienic Laboratory from September, 1927, to March, 1946. Of special interests are the following points

Of the 463 strains isolated, 377 were of human origin Of these 244 were *Brucella suis* (64 7 per cent), 92 *abortus* (24 4 per cent), and 38 *melitensis* (10 per cent), with 3 strains unclassified. Notable in this tabulation is the increase in human *melitensis* infection Also of interest is the fact that the organs of hogs yielded *Brucella melitensis* in all 12 instances, rather than *Brucella suis*

In France, 170 of 174 strains of *Brucella* were *melitensis* [659] The great majority of these came from southern France, where the disease is common among goats and sheep The patients had had

were *Brucella suis*, 38 (29.8 per cent) were *abortus*, and 1 (0.8 per cent) was *melitensis*.[204] (From this latter patient both the *melitensis* and *abortus* strain was isolated.) These findings roughly indicated the prevalence of *suis* strain infections in that hog-raising state. Many of these *suis* infections were the result of direct contact in the meat-packing industry. Some disproportion may be reflected in that *Brucella suis* is so much more readily recoverable from human blood or other source than is the *abortus* strain. The authors drew the following conclusions:

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Cases per 100,000 population in states with the highest incidence were listed, giving three-year averages, as follows.

Iowa	5 9	Maine	2 8
Vermont	5 5	Montana	2 7
Missouri	4 6	California	2 4
Kansas	4 3	Maryland	2 4
Arizona	4 2	New York	2 2
Delaware	3 5	Georgia	2 0
Minnesota	3 4	Louisiana	2 0
Connecticut	3 0	Wisconsin	2 0

Endemic occurrence of *Brucella melitensis* in Iowa was noted in 1945[354] Twenty cases of human infection had been discovered within a two-year period Of 26 strains of *Brucella melitensis*

Further studies in France were reported[661] in 1938 covering work begun in 1931 in man and animals Of 507 strains isolated from man, 477 (94 per cent) were *Brucella melitensis*, the remaining 10 (6 per cent) *abortus*.

It was felt that *Brucella abortus* was relatively unimportant as a cause of human brucellosis in France and essentially an economic and veterinary problem. Cases due to *melitensis* infections were usually multiple, occurring in localized epidemic outbreaks, whereas *abortus* infections almost invariably were sporadic and isolated

Of 869 strains isolated from animals, all were *melitensis* or *abortus;* no *suis* was encountered. Goats, sheep, and cows were the main animal reservoirs In goats and sheep infection was almost always due to *melitensis* strains. Cows were the principal hosts of the *abortus* variety, but in some regions were infected with the *melitensis* strain.

In several European countries *Brucella suis* infections in animals or man had not yet been encountered, in 1936[294]

In Malta, *Brucella melitensis* was isolated from cows as well as goats[625]

In Argentina all three species of *Brucella* are encountered in man and animals, the type of infection varying with the prevalence of goat raising (central provinces and Andean zone) or of hogs and cows (in the plains)[495] Cross-infection has been reported, as elsewhere Infection has been reported in man and animals throughout the country except in southern Patagonia

In Mexico, Castaneda, Tovar, and Velez[133] reported isolation of *Brucella* from 150 of 200 patients *Brucella melitensis* accounted for 95 4 per cent, *suis* for 1.3 per cent, and *abortus* for 3 3 per cent. These patients' infections were largely attributable to ingestion of dairy products from goats The authors pointed out that a larger percentage of *abortus* infections might have been found among the 50 patients from whom no organisms were recovered, had they used suitable CO_2 pressure in cultural work. In a group of 100 cases studied subsequently, cultural efforts were repeated when negative Eighty-four yielded positive cultures;

TABLE VII

BRUCELLA ISOLATED IN THE IOWA STATE HYGIENIC LABORATORY

SEPTEMBER 1927 TO MARCH 6, 1946 *

	Suis	*Abortus*	*Melitensis*	*Unclassified*	*Total*
Blood and clot culture	231	90	38	3	362
Milk and cream	5 [a]	67	0	0	72
Urine	3	0	0	0	3
Spinal fluid	2	0	0	0	2
Osteomyelitis	3	0	0	0	3
Spondylitis	0	1	0	0	1
Cervical adenitis	1	0	0	0	1
Pleural fluid	2	0	0	0	2
Bile	0	1	0	0	1
Ovarian cyst	1	0	0	0	1
Feces (human)	1	0	0	0	1
Calf fetus	0	1	0	0	1
Hog joint	1	0	0	0	1
Hogs (organs at slaughter)	0	0	12	0	12
TOTAL	250	160	50	3	463

* Published through the courtesy of Dr I H Borts, Director, Iowa State Hygienic Laboratory

[a] One strain isolated from improperly pasteurized milk, 4 strains from three epidemics of porcine brucellosis due to raw milk

fresh milk or milk products from these animals or direct or indirect contact with them The other 4 were *abortus* strains, the patients having histories of contact with cows. Of 54 strains isolated from cattle, 41 proved to be *abortus* These came largely from regions in the north of France, where cattle predominate, only 4 human cases were associated, occurring singly The 13 remaining strains were *melitensis,* from cows which were in contact with known *melitensis* infection of goats or sheep; human cases were associated in each instance, from 9 of which blood cultures yielded *melitensis* Of 13 strains isolated from goats, all were *melitensis* Eleven of 12 strains of sheep origin typed as *melitensis,* one as *abortus* All 3 strains isolated from horses typed as *abortus.*

Brucella suis infection, in spite of the fact that approximately 35 per cent of the pigs give positive reactions for *Brucella*. Angelini considered that the transmission of brucellosis by contact with patients was infrequent but that possibilities increase when they practice any sexual aberration which permits the access of the *Brucella* to the digestive tract. Between the ages of 1 and 4, the incidence in Mexico City is low because of use of boiled milk, children of that age seldom have fresh cheese. After the age of 5, a child begins to enjoy a certain amount of liberty in its food habits, thus explaining the increase of frequency of brucellosis with age Persons employed in domestic work (housekeepers and cooks) constituted the largest group of infected persons (44 55 per cent) apparently because they buy food either from markets or from street venders and taste the food before cooking it. Laborers were the next largest group (19 per cent) perhaps because they purchase contaminated food in small shops where they work. Students from the age of 7 years up constituted 10 5 per cent of the cases for reasons previously mentioned

Of 1,119 cultures of human origin from various parts of the world received and identified at the Central Brucella Station, Michigan State College, from 1920 to 1942, 162 (14 4 per cent) were *abortus*, 179 (15 9 per cent) *suis*, 771 (68 9 per cent) *melitensis*, and 7 (0 6 per cent) not classifiable.[351]

Of 1,003 cultures of bovine origin, 910 (90 per cent) were *abortus*, 9 (0 8 per cent) *suis*, 78 (7 7 per cent) *melitensis*, and 6 (0 5 per cent) unclassified

Of 145 cultures from hogs, 143 (98.4 per cent) were *suis* and 2 (1.6 per cent) were *melitensis*

Of 166 cultures from goats, all were *melitensis*

Of 48 cultures from sheep, 2 (4 2 per cent) were *abortus* and 46 (95 8 per cent) *melitensis*

Of 31 cultures from horses, 26 (83 8 per cent) were *abortus* and 5 (6 2 per cent) were *suis*

The 1 culture from a dog was *Brucella suis*

Of 2 cultures from buffalo, both were *abortus*

79 (94 per cent) were *melitensis* and 5 (6 per cent) *abortus*. Even if the remaining 16 patients had yielded *abortus* strains under ideal cultural conditions, the predominance of *melitensis* would have been great. They quoted the report of Tellez-Giron and Zozaya of positive skin reactions in 24 per cent of dairy cattle, 15 to 40 per cent of goats, and 30 to 35 per cent of pigs in Mexico, expressing their surprise at the very low percentage of human infection with the *suis* strain

Varying geographic and economic conditions influence the epidemiology of *Brucella* infection. For example, in Mexico City, Angelini[18] reported that the principal sources of infection were:

	Per Cent
Fresh goat cheese	42.72
Fresh cow's cheese	28.18
Cream of raw milk	12.72
Raw cow's milk	10.00
Raw goat's milk	7.27
Contact with patients	5 45
Ice Cream	1 72
Contact with animals	0 09

He pointed out that fresh goat cheese is a principal source of infection in Mexico City because the great majority of goat's milk is utilized for the manufacture of this dairy product. Fresh goat cheese is one of the principal delicacies in that city. Cow's milk frequently is mixed with goat's milk in making cheese and in that way also becomes important as a source of infection. That only 10 per cent of human infection is attributable to the ingestion of cow's milk was ascribed to the custom followed by the majority of the city population, especially the children, of drinking only boiled milk, 92 per cent of consumers boiled their milk, raw goat's milk being rarely used Of 220 cultures of *Brucella* isolated from patients by Castaneda, only 10 had the characteristics of *Brucella abortus*, 2 of *Brucella suis*, and the remainder of *Brucella melitensis* The consumption of pork sausage is very low in Mexico City, perhaps accounting for the low incidence of

Brucella suis infection, in spite of the fact that approximately 35 per cent of the pigs give positive reactions for *Brucella* Angelini considered that the transmission of brucellosis by contact with patients was infrequent but that possibilities increase when they practice any sexual aberration which permits the access of the *Brucella* to the digestive tract. Between the ages of 1 and 4, the incidence in Mexico City is low because of use of boiled milk, children of that age seldom have fresh cheese. After the age of 5, a child begins to enjoy a certain amount of liberty in its food habits, thus explaining the increase of frequency of brucellosis with age Persons employed in domestic work (housekeepers and cooks) constituted the largest group of infected persons (44.55 per cent) apparently because they buy food either from markets or from street venders and taste the food before cooking it Laborers were the next largest group (19 per cent) perhaps because they purchase contaminated food in small shops where they work Students from the age of 7 years up constituted 10 5 per cent of the cases for reasons previously mentioned

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The 1 culture from a dog was *Brucella suis*.

Of 2 cultures from buffalo, both were *abortus*

Of 11 cultures from fowl, 2 were *abortus* (18.2 per cent) and 9 were *suis* (81.8 per cent).

Of 2 cultures from rabbits, both were *suis*.

For the country of origin of these cultures, Huddleson's[549] monograph may be consulted.

URBAN AND RURAL DISTRIBUTION

Because of more frequent contact with infected animals and greater ingestion of unpasteurized dairy products, brucellosis in man is of more frequent occurrence in rural than in urban regions. (Exceptions to this rule may be expected in areas where large numbers of urban dwellers are employed in the meat-packing industry.) The common assumption that residents of cities are virtually exempt from infection because of lifelong use of pasteurized milk in their homes is fallacious. Sojourns in the country where raw milk still is sold are frequent sources of infection. Suburbs of even the largest cities are not necessarily supplied with pasteurized milk and cream. Cheese and other manufactured dairy products are still potential menaces everywhere.

AGE INCIDENCE

The belief that brucellosis is relatively rare among infants and children is founded largely on failure to consider the disease in the diagnosis of many unexplained symptoms or syndromes. Pyelitis, anemia, gastroenteritis, atypical pulmonary affections, joint involvement, unexplained fever, "malnutrition," fatigue states, and various clinical and subclinical illnesses are unlikely to be ascribed to *Brucella* infection unless all of the diagnostic methods are applied.

Hagebusch and Frei [illegible] stated that "probably the chief reasons for the apparent low incidence in children have been the difficulty in recognizing the disease and the failure to consider it as a diagnostic possibility." They reported on the observation of 182 cases in a three-year period ranging in age from 3 days to 16 years, with 95 per cent under the age of 6 and 26 in infancy. Of these 176 were chronic illnesses (p. 154).

Skin and blood-agglutination tests were made on 210 children between 4 and 15 years of age, all of whom had been drinking raw milk from an infected herd for periods ranging from five months to six years. Agglutination tests were positive in 7 of 48 tested, three weeks after they had stopped drinking infected milk.[467]

A second group of 164, tested from 6 to 12 weeks after they had ceased drinking infected milk, showed no agglutinins Intradermal tests were done in all, 27 (13 per cent) were positive, 6 (3 per cent) had questionable reactions Twenty months after the infected milk was discontinued, retesting of these 33 children showed positive reactions in 26 Twenty-six children, 3 to 18 months old, reared on evaporated milk, were used as controls, *none showed positive intradermal reactions. Positive skin reactions* were found in 9 0 per cent of 7,122 school children [21] A study of the symptoms occurring in this group of 462 reactors, as compared with 100 children of the same age group used as controls (p 244) showed evidence of chronic illness in 179 (38 7 per cent), with persistence of symptoms a year later

Paterson and Hardwick,[527] in reporting a series of 8 cases in children between the ages of 6 and 14½ years, noted the abruptness of onset in all, with symptoms referable to the upper respiratory tract, indicating the likelihood that many others occurred but [illegible]
or g [illegible]
schc [illegible]
that [illegible]
pp 153–156).

Two family groups were observed for about two years, all members of whom had been exposed at the same time to the ingestion of milk from an infected herd Of the 10 persons involved, all developed positive skin tests and positive blood-agglutination reactions All had mild illnesses characterized by aching and fever, soon after the exposure, and all promptly recovered *except one adult in one family and one child in the other.* These two developed chronic brucellosis.

Brucella suis was isolated from the blood stream of 3 children with subclinical illnesses occurring as part of an outbreak in Iowa in 1943.[71] Aside from anemia and lassitude they seemed well and did not miss a day of school. The fate of these infections was not discussed but the fact of their occurrence throws some light on the controversial question of the incidence of brucellosis in childhood. Many such "subclinical" or mild illnesses unquestionably remain undiagnosed. They cannot be said to be unimportant since clinical and severe degrees of illness may supervene at a later date.

Deaths and death rates are tabulated as to age in the chapter on prognosis (Table X, p. 415).

SEX INCIDENCE

The sex incidence may be considered as about equally distributed except in those occupational groups in which males are exposed by direct contact with infected animals, living or dead, to a greater extent than are females. Cesari[185] noted the higher incidence in men where milking of goats was done by men and the higher incidence in women when they were the milkers.

Mortality statistics for the United States throw some light on sex incidence, among 506 deaths, 289 were males and 164 were females (see chapter on prognosis—Table X).

SEASONAL INCIDENCE

Seasonal variation is likely to occur in the acute illness in those groups who are directly exposed to infected animals Outbreaks of milk-borne infection may also be greater in spring. This may be attributable[294] to the heavier exposure during and following the farrowing and calving seasons when there is an increase in the excretion of organisms In the chronic illness, with its usual insidious onset, seasonal variation is less likely to be noted.

EPIDEMIC BRUCELLOSIS

Multiple cases of acute or chronic brucellosis are not unusual in a family or community when the raw milk is from a single

infected cow or a heavily infected herd. Dilution of infected milk in herds in which there are few infected cows is apparently an important factor in preventing large outbreaks in communities where raw milk is used.

All members of the family using milk from a single infected cow are likely to contract the disease in mild to severe form, [illegible]

weeks [illegible] There were 4 children ranging in age from 2 to 14 All developed blood-agglutination reactions, the adults being ill much longer than the children

In a family of 7 persons under observation of the author, the father, mother, and 4 of the 5 adult or adolescent children showed laboratory evidence of *Brucella* infection, past or present. One adult daughter was clinically ill, with choroiditis apparently attributable to brucellosis, the mother had a chronic rheumatoid arthritis which may have been of *Brucella* origin. Two of the children gave histories suggesting mild chronic brucellosis a year or more previously but had been well since. The father and other child were free of symptoms or history of illness All had had raw milk at their country home where cows were kept by their tenant farmer As far as was known no abortion had occurred in the small herd

In the family of a physician practicing in a rural community where raw milk was obtained from either of two small local dairies, from 1921 to 1933, 3 of 6 in the household developed low-grade clinical brucellosis—one servant, a nurse, and the 4-year-old daughter The physician's wife developed a prolonged illness with cough and low-grade fever, at first thought to be tuberculosis This was later ruled out but tests for brucellosis were equivocal The physician and the other servant developed no clinical or laboratory evidence of the disease

A milk-borne outbreak of *Brucella suis* infection among 77 persons in a town of 1,200 persons in Iowa was traced to a raw milk supply in 1943 [74] In one family all 6 members were ill, in another,

6 of the family of 12. There were no fatalities. Both laboratory and clinical findings suggested a *Brucella suis* strain of relatively low virulence. Blood of 29 patients was cultured; 13 (45 per cent) yielded *Brucella suis*. *Brucella suis* was isolated from the milk of 2 of the sows on the dairy farm where they mingled with the cows; 11 of 24 tested showed positive agglutination reactions.

Farber and Mathews [209] reported an epidemic of 26 cases of brucellosis traceable to an infected dairy herd on a college campus in Indiana.

An outbreak of 6 cases in a town of 5,387 population in southern New Jersey in 1931 was traced to raw milk from one dairy; no new cases occurred after pasteurization of the milk supply.[816]

Sharp [620] quoted an outbreak in which he stated that 40 of 160 patients (25 per cent) in one community had died.* He was confusing the data quoted by Aubert, Cantaloube and Thibault [30] who actually had stated that 40 of 106 patients (38 per cent) *had been reported by a Paris newspaper to have died.* Their own investigation had revealed a disseminated outbreak spread over several communities in which the morbidity rate was high but the mortality rate not over 7 per cent.

Horning [412] reported a smaller outbreak of *Brucella suis* infection from cows with high mortality in 1935 in which there were 14 cases with 3 deaths (21 per cent) among elderly inmates of an institution in Connecticut.

Cruickshank and Stevenson [112] reported an outbreak of 4 cases of infection with fever among 54 girls in a boarding school in England in which a raw milk supply had recently been introduced. Ellington and his associates [103] in 1940 reported an outbreak in a boys' school in England in which 2 febrile cases, 26 "mild infections" and about 130 "latent infections," occurred among the 400 students, also after evacuation to the country where consumption of raw milk was begun Eighteen of the 26 boys ran a febrile course. *Brucella abortus* was isolated from the milk of cows furnishing a part of the school's milk supply They

* This quotation from Sharp's report appeared in the first edition of this monograph

referred to von Engel's report in 1938 of an outbreak in a hospital in Hungary and Giani's report of an outbreak in Italy.

Mazza [165] stated that a mortality rate of 35 per cent occurred in one province of Argentina.

Beattie and Rice [46] reported a milk-borne epidemic of 30 cases in Iowa, with no deaths.

It is apparent that virulent outbreaks with high mortality are rare but that milder outbreaks are relatively frequent.

Chapter IV

PATHOLOGY

As they [*M melitensis*] have been grown as pure cultures from the spleen by inoculation on agar-agar in 25 instances, from splenic blood obtained during life in 2 instances, and from the spleens of inoculated monkeys after death in 3 instances, there can be little doubt that the spleen is one of the places where the microorganism is invariably present in cases of this fever, a fact further probable when we consider the naked-eye appearance of the spleen at post mortem examination In the liver and kidney it has been found, and we must next search for it in the lung, intestine, cerebrospinal system, and in the swollen joint, before its pathology can be placed on a sound footing (David Bruce, quoted by Hughes, 1897 [369])

BECAUSE of the comparatively few deaths from brucellosis, most observers have had to content themselves with operative findings, radiographic changes, and clinical observations to describe the pathology. In current literature, pathologic processes are usually listed under physical findings, localized lesions, or complications Since pathologic findings are usually so incomplete, isolated findings of various observers are abstracted. There is some tendency toward uniformity in reports in recent years Gross and microscopic pathology ultimately may be elucidated so that they can be utilized as diagnostic criteria in biopsy and necropsy specimens

large acid-fast bacilli were found in the examination of several sections. *A guinea pig inoculated with this material developed tuberculosis and cultures yielded* Brucella. From a small cyst in the right ovary and from enlarged glands in the broad ligaments *Brucella* was present in pure culture. The appendix was slightly enlarged and fibrous, and the ileocecal glands were much enlarged. These tissues likewise yielded *Brucella* On the meso-appendix and the mesentery over the serous coats of the intestines and on the peritoneum were many papules presenting a picture of tuberculous peritonitis The white papules were softer than tubercles The histologic picture resembled tubercles with giant cells and lymphoid infiltration but there was less fibrous tissue than in the ordinary tubercle. No tubercle bacilli were seen and none were recovered by guinea pig inoculation, but a pure culture of *Brucella* was obtained from them and from the cystic right ovary.

Hemorrhagic ovarian cysts yielded *Brucella* in another patient reported by Amoss. This patient's bile also yielded *Brucella* after duodenal drainage. At operation *Brucella* was again recovered from the bile and also from the posterior wall of the gallbladder. He reported a second instance of gallbladder infection, at operation the gallbladder (which had showed no abnormality on x-ray examination) showed a much thickened posterior wall adherent to the liver.

The following postmortem findings were reported by Hardy, Jordan, Borts, and Hardy.[205]

H.G , a 21-year-old male packing-house employee, died of brucellosis of the *suis* variety after an illness of three months The abdomen contained 2 liters of clear serous fluid, the pleura 1 liter on each side, and the pericardium 300 cc. The heart was about twice its normal size, weighing 597 Gm. On removing the heart an abscess in the anterior mediastinum the size of a hen's egg and containing bloody pus was opened The aorta showed an erosion 1 cm in diameter and the anterior cusps were destroyed A mass 3 cm in diameter occupied the sinus behind the valve and connecting with the abscess in the mediastinum The liver was markedly enlarged and of the nutmeg type The spleen was enlarged, but on section no unusual pathologic changes were noted *Anatomical findings* Reticulo-endothelial hyperplasia of

Chapter IV

PATHOLOGY

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phoid hyperplasia throughout the spleen, sinuses were dilated and contained numerous macrophages and a few multinucleated giant cells

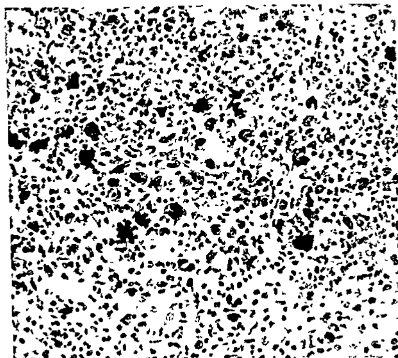


Fig 5 Granuloma of brucellosis in the liver, ×340 Most of the numerous giant cells strongly suggest enlarged megakaryocytes, while others are of epithelioid cell character (Courtesy of Dr S M Rabson and *Am J Clin Path*)

Rabson [534] reported general visceral congestion and evidence of continued breakdown of red cells at necropsy in a 28-year-old farmer who became ill soon after suffering a compound fracture while working in a barnyard [557] Bone marrow, enlarged liver and spleen, and splenic vein were sites of granulomas These showed the usual picture of epithelioid cells, lymphocytes, and giant cells, many of which were multilobulated, resembling enlarged megakaryocytes (Figs 5 and 6)

lymph glands, central lobular necrosis and degeneration of liver, acute toxic nephrosis.

Mrs. H.B., aged 57, died after an illness of eight months. *Anatomical findings:* chronic interstitial pancreatitis, chronic cholecystitis; fatty infiltration and passive congestion of the liver; fragmentary myocardial degeneration. This patient had had positive blood-agglutination titers of 1:640 and 1:1280. No cultures were undertaken.

Mr. W.B., aged 27, a farmer, died after an illness of five months. Blood specimen showed agglutination with *Brucella abortus* in a 1:320 dilution. *Both* Brucella abortus *and* Brucella suis *were isolated from blood.* A lung abscess was drained. It could not be said whether both of the varieties of *Brucella* were primarily involved in the production of the lung abscess

They summarized their findings as follows:

In 5 cases death occurred without clinical evidence, in 1 case without pathological evidence, of any complication or localized infection, there was involvement of the cardiovascular system in 3 instances revealing evidence of malignant endocarditis in 2 of these, in 1 a lung abscess occurred, in another the gastrointestinal system was mainly involved The etiologic relationship of *Brucella* to the production of these fatal complications was uncertain. It is to be noted that some cases which began as the intermittent or ambulatory type terminated fatally as well as those which from the first were of malignant nature.

Autopsy findings[544] in another case of fatal brucellosis were as follows: Grossly, there were ascites, pericardial effusion, pleural effusion, flabby myocardium, basal confluent lobular pneumonia, chronic passive congestion and chronic edema of the lungs, atrophic liver with greyish nodules on its surface with marked increase of connective tissue, chiefly perilobular. Microscopically, liver showed chronic passive congestion, patchy fatty infiltration, irregularly distributed chronic parenchymatous hepatitis of the type of atrophic cirrhosis. *Pancreas* showed diffusely scattered pinhead-size reddish, translucent nodules on the splenic surface somewhat resembling tubercles, microscopically these were localized areas of perisplenitis with hyaline changes. There was lym-

tous form enlargement of the lymph nodes and splenomegaly were the commonest features.

Resemblance to the Tubercle

Proliferation of the cells of the reticulo-endothelial system was commented on by Sharp[620] as "the most essential item in the general pathologic alteration." He felt that it may be sufficiently distinctive to help differentiate the disease from other conditions. In studying necropsy specimens he observed that "a more or less definite type of infectious granuloma is suggested, the most striking feature of which is a nodular lesion resembling the tubercle," occurring in animals more regularly than in human autopsy specimens Necrosis was absent in the nodular areas in man but may occur in other organs not showing nodular reaction such as in hepatic cells where little but an empty framework of connective tissue and persisting capillaries is left. He quoted Wohlwill's description of nodules somewhat smaller than millet seeds and of fairly uniform structure, overbalanced by the presence of "large epithelial cells having clear, moderately coarse eosinophile, finely granular, or in any case not generally homogeneous, protoplasm and pale nuclei with scant chromatin." In a few of the nodules were occasional giant cells, some resembling Langhans' cells, or having nuclei scattered irregularly. Fat occurred in fine droplets in the epithelial cells. He noted no tendency to caseation. Rossle had noted that the cellular aggregations were not always in defined nodules and that the defined nodules had not always a similar aggregation Some lesions with a superficial resemblance to the tubercle were dissimilar in the microscopic structure. Gregerson and Lund had observed no epithelioid cells but stated that the nodules consisted of simple fibroblasts, and lymphocytes scattered in the fibrous layer. Rothenberg[559] noted a perisplenitis showing translucent nodules of pinhead size, with hyaline changes, scattered over the splenic surface Nodular reactions were also found in lymph glands, bone marrow, and other tissues Hansmann and Schenken[295] described meningeal nodules.

Forbus[229] stated that the reticulo-endothelial system is the primary reacting mechanism, the lesions belonging to the general group of infectious granulomas; although the infection is essen-

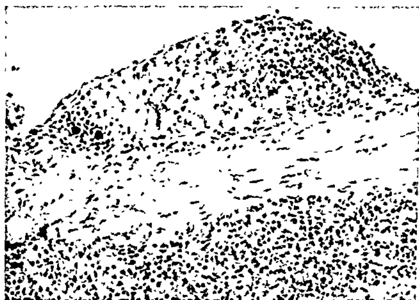


Fig 6 Granuloma of brucellosis in the intima of a vein within the spleen, ×158 The endothelium is lifted by the granuloma but is not injured (Courtesy of Dr S M Rabson)

tially a generalized one, its clinical and anatomic expressions may be focal or localized Since intermittent bacteriemia is a constant feature of brucellosis, extravascular foci of bacterial propagation must exist He described three types of fatal brucellosis: (1) the septicemic or relatively acute form, (2) the focal or localized form, also relatively acute, (3) the chronic lymphogranulomatous type with a prolonged course In the septicemic type there was little that was specific for *Brucella* infection, the findings being those of almost any bacteriemia with pronounced intoxication The focal or localized infections particularly noted were vegetative endocarditis, meningitis, orchitis, and involvement of vertebral and metatarsal bones and joints. In the lymphogranuloma-

The lesions were not considered to be embolic but due to elimination of *Brucella* through the glomerulus

Castaneda [131] experimented with the three varieties of *Brucella* in guinea pigs and rabbits *Brucella* were found in the cytoplasm of macrophages and fibroblasts and, especially in the spleen, in *endothelial and reticular cells, in parenchymatous cells of the* kidney, and in interstitial cells of the testes.

Nyka [616] stated that *Brucella* develop in mesenchymatous cells (polymorphonuclear leukocytes and macrophages, endothelial cells of capillaries, young fibroblasts) and in parenchymatous cells (liver cells, epithelial cells of the tubules of the kidney, cells of the cortex of the adrenal gland, interstitial cells of the testes, and alveolar cells of the lung). Some differences were noted in the selectivity of various types of *Brucella* for certain cells, *Brucella melitensis* and *abortus* developing more abundantly in the alveolar cells of the lung of mice than *Brucella suis* He stated that the lesions found in animals and man were produced by *Brucella* and not by secondary infection or any allergic influence.

Localized Pathology

HEART AND BLOOD VESSELS

Pericarditis

Brucella has often been isolated from pericardial fluid at autopsy, the fluid usually being increased in amount (p 174).

Endocarditis

Vegetative endocarditis, involving the mitral valve in 3 patients whose splenic cultures were positive, was reported by Hughes,[369] with autopsy findings. He cited Hewlett's report of histologic sections of 1 case with almost completely organized vegetation and round-cell infiltration of the mitral valve *Aortic endocarditis* was reported by Matstoff (cited by Sprunt and McBryde) [815] with parenchymatous degeneration of the heart muscle De la Chapelle [169] reported vegetative endocarditis associated with or

Fleischner and Meyer[222] suggested that the anatomic lesions in guinea pigs infected with bovine abortion disease might well have been called tuberculous in early testing of milk samples.

Carpenter[118] stated that the cellular reaction of the tissues of man and of experimental animals is typically granulomatous and particularly like that of the tubercle. Microscopically, the lesions caused by *Brucella abortus* show central areas of epithelioid cells surrounded by lymphoid cells. Giant cells may occasionally be observed but they are not so prevalent as in the typical tubercle.

It will be seen from the foregoing that there is general agreement as to resemblance of *Brucella* pathology to that of tubercle bacillus infection, but with no uniformity of opinion as to how nearly identical are the two processes.

Multiplication of Brucella Within Cells

Castaneda[131] called attention to the early observations of Smith,[639] who demonstrated *Bacillus abortus* within the cytoplasm of epithelial cells of the chorion of the aborting cow in 1919. Smith considered that intracellular multiplication was taking place. His findings were confirmed by Goodpasture and Anderson[286] in 1937, who found that *Brucella* multiplied within the cytoplasm of certain cells more intensely than extracellularly. Buddingh and Womack[95] noted that *Brucella abortus* and *suis* had a tendency to select certain cells of mesodermal origin, while the *melitensis* variety was found only in ectodermal cells. All three species were not merely phagocytized but they actually multiplied within the cytoplasm of the macrophages. They advanced the theory that the monocytes acting as a natural means of defense against the infecting agent, supplied a favorable refuge where multiplication took place and therefore constituted the source of continual infection from cell to cell.

The intracellular position of *Brucella* in infected tissues in man was first described by Meyer.[482] He noted metastatic lesions in the kidney, the organisms developing in the epithelium of Bowman's capsule and the proximal end of the convoluted tubules

due to *Brucella* infection as did others, all with postmortem study.[5, 125, 167, 269, 288, 295, 439, 554, 583, 598, 618, 638, 645, 646, 698]

De la Chapelle's[169] report included postmortem findings of vegetative and ulcerative endocarditis of the aortic valves. Because of the clinical course, during which *Brucella melitensis* was isolated from the blood, and the absence of evidence of old rheumatic heart disease, he considered it one of true infection of the valves with *Brucella*.

Spink and Nelson,[645] in reporting 1 case of their own in 1939, stated their belief that many cases reported as *Brucella* endocarditis were in reality *Brucella* bacteriemia associated with rheumatic endocarditis, in agreement with Albertini and Lieberherr.[5] The patient reported by Scott and Saphir[618] had had blood cultures repeatedly positive for *Brucella abortus* but the postmortem examination showed rheumatic heart disease, a history of rheumatic fever preceded that of *Brucella* infection. Spink and Nelson[645] were able to find reports of but 2 cases of endocarditis caused by *Brucella* that they considered were substantiated by sufficient bacteriologic and anatomic evidence at necropsy, prior to their own case. One of these has been reported by Casanova and D'Ignazio in 1933[128] The organism (*Brucella melitensis*) had been isolated from blood before death, at autopsy fresh vegetations were found on the aortic valve and a pure culture of *Brucella* was recovered from the vegetation. The other case was that of Rothman,[589] at autopsy there was marked destruction of the aortic valve with fresh vegetations from which *Brucella abortus* was recovered In both cases cultures obtained produced typical lesions of *Brucella* infection in guinea pigs. Several other reported cases had sufficient bacteriologic evidence of *Brucella* infection to warrant a probable diagnosis of *Brucella* endocarditis. The cases reported by De la Chapelle[169] and by Levy and Singerman[439] were considered to be unproved since *Brucella* had not been isolated from the valves and identified by cultural and serologic methods. (However, the case of Levy and Singerman did yield Gram-negative bacilli in smears of mitral vegetations)

Spink and Hall's case, a 29-year-old farmer, was authenticated

by isolation of *Brucella abortus* from the vegetation on the aortic valve and from kidney, spleen, heart's blood, and lungs. Blood-agglutination reaction during the illness had been positive in high titer. Blood cultures had been negative. *Skin test had been negative.* The inadvisability of using Gram-Weigert stain in differentiating Gram-negative and Gram-positive organisms in tissue preparation, because of confusion with other organisms such as streptococcus viridans, was mentioned

Smith and Curtis[635] reported a fatal case of brucellosis with endocarditis Blood cultures prior to death had yielded *Brucella abortus* and an ulcerovegetative process was found at autopsy. There was an old history of probable rheumatic fever and the authors commented that the ulcerovegetative endocarditis found at postmortem was "on previously existing aortic scars." They considered it probable that *Brucella* organisms lodged and vegetated upon the valves scarred by an old valvulitis.

In a second proved case of *Brucella* endocarditis in a 36-year-old farmer Spink and his associates[646] reported isolation of *Brucella abortus* from blood, heart vegetation, spleen, ovary, hilar lymph nodes, lung, and pericardial fluid The findings were. subacute *Brucella* endocarditis, subacute myocarditis, old rheumatic heart disease with mitral stenosis, aortic stenosis and regurgitation, embolism to the left middle cerebral artery, and left parietal encephalomalacia, mononuclear pneumonia, pulmonary edema and congestion, infarction of kidney and spleen, subclinical glomerulonephritis

Quintin and Stalker's[594] case was described as *Brucella abortus* ulcerative vegetative endocarditis superimposed on old rheumatic valvular disease The myocardial, splenic, and renal lesions seen at autopsy were ascribed in part to emboli from the vegetations and in part to bacteriemia The patient was a 26-year-old farmer who became ill in December, 1942, and died in November, 1943 Blood-agglutination reaction was positive in a 1 250 dilution. *Brucella abortus* was isolated from blood Physical examination had showed evidence of mitral stenosis, probably attributable to rheumatic fever in 1

Postmortem findings were: Hydrothorax and hydroperitoneum; moderate enlargement of liver with nutmeg appearance on cut section, marked enlargement of spleen with multiple infarctions, subacute diffuse pyelonephritis with minute abscesses, enlargement of both ventricles and left auricle of the heart with elevated hemorrhagic areas. The tricuspid valve showed patchy fibrotic thickening of the cusps. The pulmonary valve showed small petechiae. Necrotic areas were found in the hypertrophied left ventricular wall. The cusps of the mitral and aortic valves were sclerosed. The right posterior cusp was involved in a large polypoid vegetation which almost occluded the orifice. The anterior cusp was destroyed by vegetative growth. The intima of the aorta was roughened near the cusps.

Microscopic sections showed abundant collections of Gram-negative minute bacteria along the periphery of the vegetations and surrounding the abscess cavity in the epicardium of the left ventricle, with a mycotic aneurysm in the left ventricular epicardium and myocardium

Culture *Brucella abortus* was recovered from pericardial fluid and heart blood

Coexistence of acute bacterial endocarditis and *Brucella* septicemia was reported to the author by Hauswirth [313] because of the unusual origin of the infection (p 52). The patient, a 55-year-old physician, died after thirty-six days of pyrexial illness. Blood-agglutination reaction with *Brucella* was positive in a dilution of 1 · 200 on the thirteenth day Skin test subsequently was positive Blood culture was negative for *Brucella* throughout the illness but was positive for hemolytic streptococcus on the twenty-fifth day, on which date petechial spots were noted. Evidence of acute bacterial endocarditis, principally of the aortic valve, apparently of streptococcic origin, was found on postmortem examination *Brucella melitensis* was isolated from blood collected at autopsy and from a remaining portion of Italian cheese, part of which the patient had ingested about a month before the onset of his illness

Wechsler and Gustafson [illegible] reported a case of *Brucella* endocarditis of a congenital bicuspid aortic valve in a white male patient of 28

Disease of Blood Vessels

Rupture of a mycotic aneurysm of the basilar artery in a patient with *Brucella* meningo-encephalitis, with autopsy findings, was reported by Hansmann and Schenken in 1932.[288]

The aneurysm, 9 × 6 × 6 mm, arose from the dorsal surfaces of the proximal portion of the basilar artery. A short pedicle containing a channel 1 mm in diameter connected the lumen of the sac and the artery. Most of the meningeal vessels showed a thickened adventitia, heavily infiltrated with inflammatory cells. Several of the brain-stem vessels showed marked displacement of the media or connective tissue with marked subintimal connective-tissue proliferation. Inflammatory cells were present throughout the entire thickness of the walls. Where branches of the meningeal vessels pierced the cortex, a perivascular collar of inflammatory cells accompanied the vessels. Many of the cortical and subependymal vessels showed perivascular collections of lymphocytes. The phenomenon was virtually confined to these two areas of brain substance. One submeningeal area showed vacuolization of cells, edema, and phagocytized hemosiderin, inflammatory cell infiltration and snarled glia. The other was a more recent collection composed largely of large mononuclear cells, lymphocytes, and cellular debris. A hyalin thrombus was noted in a small vessel.

Rupture of a mycotic aneurysm of the left femoral artery, in a 45-year-old farmer with an endocarditis and bacteremia due to *Brucella suis* infection was reported by Degowin, Carter, and Borts,[167] together with postmortem findings. The rupture of the aneurysm was in the region of the internal ligament. Blood had extravasated into retroperitoneal tissues along the left abdominal wall as far as the diaphragm, into the mesentery, and into the scrotum. The heart showed valvular sclerosis with vegetations involving the mitral valve. *Brucella suis* was isolated in pure culture from the vegetations, from the endocardium, and from the walls of the aneurysm.

Damage to the endothelial lining of blood vessels with extravasations in the subperitoneal connective tissue and throughout the intestines was noted by Eyre[207] in *melitensis* infections.

Others have noted hemorrhage in the absence of ulceration. The author[300] has reported hemorrhage into both Bartholin's glands in a patient with brucellosis complicated by pyelitis, but not con firmed by culture. *Phlebitis* and *panarteritis* have been referred to as possibly attributable to *Brucella* infection (p. 175–176).

Endarteritis due to *Brucella* infection was suggested by the author[302] as a possible cause of some cases of coronary artery disease in 1941. In 1942 Manchester[459] mentioned endarteritis of *Brucella* origin as a possible cause of coronary artery disease and of temporal arteritis. Kilbourne and Wolff[400] reviewed the known findings and possible etiology in temporal arteritis and noted its usual association with infection (periapical tooth infection, ulceration of the gum, "sore throat," recent extraction of diseased teeth) There was a panarteritis nodosa, with hypertrophy of the intima and media, and necrosis associated with the formation of granulomatous tissue, foreign-body giant cells, periarterial cellular infiltration, eosinophilic invasion, and thrombus formation. Unlike the findings in periarteritis nodosa, there were giant cells but no aneurysmal dilatations The presence of giant cells suggested a tuberculous etiology but no tubercles were seen and no acid-fast bacilli demonstrated. (The similarity to a tuberculous process suggests further study from the standpoint of possible *Brucella* infection in view of the known similarity between some *Brucella* and tuberculous lesions)

Thrombophlebitis had been reported in 1914 by Cantini[111] and by Wohlwill[720] in 1932 Wohlwill reported the death of a woman from pulmonary embolism in whom an embolus from the femoral vein was seen to plug the main branch of the pulmonary artery at necropsy Death from a pulmonary embolus in a patient suffering from acute brucellosis was reported in 1936 by Bagley, Mueller, and Wells.[34] At autopsy antemortem clot was found in the left pulmonary and right pulmonary arteries and a thrombus in the left femoral veins, with no inflammatory changes in the veins. Phlebitis and pulmonary embolism had been reported by Roger and Audier[581] in 1935; they considered that venous local-

ization of *melitensis* septicemia occurred. Rabson[555] noted granulomas in the splenic vein.

BLOOD

Blood changes of a significant but not uniform pattern have been noted by many The most common finding is a slight to marked leukopenia, with relative lymphocytosis Eosinophilia, of slight to extreme degree, may be found presumably as an allergic response to *Brucella* infection.

Hardy, Jordan, Borts, and Hardy[293] noted markedly low white blood counts In one patient a white count of 2,950 with 32 per cent polymorphonuclears, 19 per cent small lymphocytes, and 50 per cent large mononuclears was noted In another patient there was a marked leukopenia, the white blood count on two occasions being 2,150.

Blood changes are discussed more extensively under symptomatology (pp. 177–180).

LUNG

Congestion with lobular consolidation of the bases and pleuritic effusion and adhesions in others was described by Hughes.[367] Hardy and his associates[295] described pleural effusion and adhesions in one fatal case and lung abscess in another. In the latter case both *suis* and *abortus* strains had been isolated from blood (p 94)

Eyre[207] stated that pneumonia in brucellosis is generally due to secondary infection with the pneumococcus but pointed to the case of Fiorentini, in which *Micrococcus melitensis* was isolated from the sputum, as evidence that occasionally pneumonia may be due to *Brucella* infection primarily. Isolation of *Brucella* from the sputum has also been reported by Vanni[680]

Cases of bronchial and lobar pneumonia have apparently been due to *Brucella* infection[47, 278, 424] The author encountered 2 patients with pneumonia apparently due to brucellosis (p. 170). In one, a Maltese, there was the more or less characteristic fan-shaped hilar infiltration (Fig 7), noted by Beatty and by Lafferty

and Phillips. In the other patient the illness was an extremely diffuse bronchopneumonic process involving both lung fields in their entirety, giving the radiographic appearance of pulmonary



Fig 7 Lobar pneumonia, apparently of *Brucella* origin (Harris, H J, *Bull N Y Acad Med* 19 631, 1943)

carcinomatosis or miliary tuberculosis Production of thin mucoid expectoration averaged about 24 ounces daily (Fig 8)

Two distinct types of lung lesions were found in a fatal case of brucellosis with extensive lymph-node involvement [526] The greater part of them were peribronchial and endobronchial Within the bronchioles were great collections of polymorphonuclear leukocytes and inflammation of the bronchiolar epithelium (bronchiolitis). In the peribronchial region were large collections of round cells and polymorphonuclear leukocytes, the inflamma-

tory process not penetrating any great distance beyond the bronchioles. There were areas of reticulo-endothelial proliferation scattered throughout the lungs, especially in the interlobar pleura,

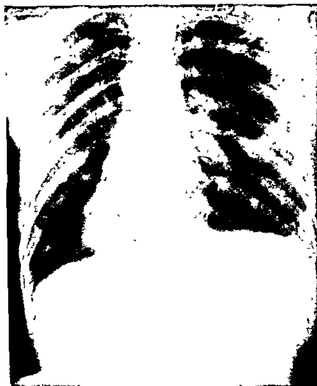


Fig 8 Diffuse *Brucella* bronchopneumonia simulating miliary tuberculosis or carcinomatosis (Harris, H J, *Bull N Y Acad Med* 19 631, 1943)

occasionally surrounding a blood vessel, sometimes surrounding a bronchiolar lesion, and frequently in the lymphatics There was hyperplasia of the lining membrane of the lymphatics themselves in the involved interlobar pleura

SPLEEN

Hughes[364] quoted Bruce's autopsy reports of enlargement of malpighian bodies in the spleen, apparently due to lymphoid-cell

hyperplasia, and swelling of the endothelial plates of the marginal *sinuses, with a few micrococci. Eyre*[297] *reported the spleen at* autopsy as always increased in weight and usually soft and friable, the main microscopic changes being an increase in the lymphoid *cells and large endothelial cells containing ingested red cells* De la Chapelle[167] reported enlargement of the spleen with scattered areas of necrosis in a patient who died of a *melitensis infection. Sprunt and McBryde*[619] *reported a large number of* phagocytic cells filled with hemosiderin in the splenic pulp, relatively small and inactive malpighian corpuscles, and a positive culture of *Brucella* in a 4-year-old boy who died of *Brucella* infection, complicated by a terminal staphylococcus infection Sharp[620] described nodular reactions, often resembling tubercles, as being most clearly defined in the spleen Enlargement, with increase in weight up to 1.58 kilograms,[43] is frequently found at autopsy, at laparotomy, and on physical examination.

Splenomegaly is not a constant finding Involvement is most likely to occur in the severe infection, particularly with the *melitensis* strain, and *is uncommon in the mild chronic illness.* Peritoneoscopy will allow visualization of the spleen when it is not palpable In one of the author's cases perisplenitis was so *diagnosed, the omentum was adherent to and almost completely* wrapped around the spleen which was of normal size In a second patient in whom the spleen also was not palpable definite enlargement was noted through the peritoneoscope

Enlargement results from lymphoid hyperplasia according to many observations The semifluid consistency described by Hughes[480] in some autopsy specimens has been thought by others to have been at least partially due to postmortem changes Tubercle-like *translucent pinhead nodules, with hyaline changes,* scattered over the surface of the spleen were described by Rothenberg.[illegible] A preponderance of large lymphocytes and mononuclear cells infiltrating around the vessels was described by Archibald[24] in smears of splenic pulp Passive hyperemia is common.[620] Intense congestion with sinuses enormously distended with blood was described by Bruce,[97] small hemorrhages by Bassett-Smith,[42]

organized thrombi in trabecular veins by Gregerson and Lund,[275] and anemic infarcts by De la Chapelle.[169] Well-demarcated areas of infarction, with evidence of acute splenitis and congestion, with focal areas of necrosis and cellular infiltration, was reported by Wechsler and Gustafson.[693]

Forbus[243] stated that the spleen shows gross lesions like those of the involved lymph nodes. It may weigh as much as six or seven hundred grams, with both diffuse and focally altered structure. The pulp is abundant and has the gross appearance that is typical of the acute splenic tumor found in all general infectious processes. The focal lesions are poorly demarcated, grey, homogeneous, slightly indurated nodules, difficult to differentiate grossly from swollen and enlarged malpighian bodies when small The larger focal lesions resemble tubercles in which necrosis and caseation has not yet occurred, many may coalesce and produce large lesions in which focal necrosis and hemorrhage are conspicuous, resembling anemic infarcts. When necrosis is chiefly coagulative the pigmented indurated lesions are not unlike those of Hodgkin's disease.

In the case of Degowin, Carter, and Borts[167] (p 103) the spleen weighed 950 Gm, the organ was softer than normal, and cut sections of malpighian bodies were enlarged, the parenchyma extremely pultaceous, with an area of yellow necrosis near the lower pole, surrounded by a zone of hyperemia, with similar zones near the upper pole The splenic follicles were hyperplastic, containing small, hyalinized areas near the center There was diffuse hyperplasia of the reticulo-endothelial elements Throughout the pulp were clusters of loosely arranged plasma cells, lymphocytes, and large mononuclears in no definite pattern, poorly circumscribed, blending with the surrounding pulp There were areas of congestion and the sinusoids were conspicuous A large mass of scar tissue in one region contained old blood, pigment, and scattered round cells In another section was a large area of infarction, surrounded by a wide zone of extravasated blood Fibroblastic proliferation was extensive at the periphery of the infarct No organisms were found in stained smears but inoculation of

guinea pigs resulted in recovery of *Brucella suis* from all organs.

Mazza and Jorg[406] described splenic changes with hypertrophy of the malpighian bodies due to the disappearance of the germinal centers, the nodules themselves being small with ill-defined outline. In the red pulp were noted a variable degree of active or passive congestion, hyperplasia of the splenocytes with epithelioid hypertrophy or myeloid infiltration, proliferation of the connective tissue, and large hypochromatic zones, among the lymphatic nodules and the remains of Billroth's cords, larger when there was more congestion and fibrosis. The lesions were described as splenitis with clear areas, combined with diffuse epithelioid hyperplasia of splenocytes originating from the endothelial cells of the sinuses. They considered that no other lesions of the spleen presented themselves so constantly in the same combination.

Spink,[641] having removed the spleen of a patient with chronic brucellosis with positive blood culture, was able to demonstrate typical granulomatous changes but was unable to isolate the organism from splenic tissue

PERITONEUM

Peritonitis simulating tuberculosis was described by Amoss[16] as showing discrete white papules on the meso-appendix, mesentery, serous coats of the intestine, and on the parietal peritoneum. Histologically these papules resembled but were softer than tubercles, with giant cells and lymphoid infiltration, and with less fibrous tissue *Brucella* was isolated in pure culture

LIVER

Hepatitis

Hepatitis is perhaps of more common occurrence than splenitis Bruce[illegible] and Hughes[illegible] described extensive liver changes in some autopsy specimens

Sharp[illegible] discussed the tendency to necrosis and mentioned the degeneration about the central veins reported by De la Chapelle,[169] and the central lobular necrosis reported by Hardy and his associates[295] Wohlwill[illegible] reported an extreme degree of ne-

crosis in patches where only the empty framework of tissue was left.

A small round nodule about 1 cm in diameter was removed from the parenchyma of the liver at the base of the adhesions extending from the diseased gallbladder which had been excised (p. 115).[478] It was rounded, white, and fibrous, with central softening and a granulomatous appearance Semipurulent material was expressed and yielded *Brucella melitensis* on culture. The same organism was recovered from the blood prior to operation and from the gallbladder wall after cholecystectomy Microscopic examination showed a bizarre, destructive, inflammatory process in varying stages. The cellular reaction centered about a granulomatous process 15 mm in diameter, the center of which consisted of purulent material, disintegrating polymorphonuclear leukocytes, and cellular debris. This was surrounded by a vascular connective-tissue wall, epithelioid cells, and lymphocytes, among which were occasional small nucleated giant cells Around the central lesion there was infiltration with lymphocytes and plasma cells, about the portal channels was an inflammatory proliferation of the epithelium of the bile ducts. Some of the lesions were in an early stage and showed a few neutrophiles and eosinophiles in the triad spaces Around the intervening hepatic parenchyma there were numerous small, discrete, tubercle-like foci which consisted of lymphocytes, epithelioid cells, and an occasional small giant cell All foci were surrounded by a proliferative reaction of fibrous tissue which tended to encapsulate them. On examination of stained histologic sections small Gram-negative rods occurring singly and in pairs were noted Culture yielded *Brucella melitensis*

In the autopsy case reported by Degowin and his coworkers [167] (p 103), the liver was friable and brownish-yellow. On cut section, the architecture was distorted by yellowish-grey, slightly elevated areas in the central zone of the lobules. Microscopically there was evidence of widespread parenchymal injury, with atrophy, degeneration, and extensive necrosis of the liver cords, most marked in the central zone but in many places extending

to the mid-zone and portal areas. There was fatty metamorphosis, with large amounts of lipochrome and hemosiderin-like pigment. Islands of regenerating hepatic cells showed distortion of the architecture. Round cells and a few mononuclears were scattered throughout, in many places forming small nests in the areas of degeneration. No organisms were found in the stained tissues but were recovered from guinea pigs inoculated with saline suspensions made from the liver tissue.

Mazza and Jorg[468] considered liver involvement as hepatitis, with alteration of an inflammatory nature, usually with macroscopic foci of central lobular fatty degeneration which may be foreign to *Brucella*, perhaps due to some type of malnutrition and lack of lipotropic factors. They described infiltrative but more often necrotizing lesions, the latter a nodular type conforming to those described by others but without multinucleated giant cells resembling tuberculous lesions The diffuse type was characterized by devitalization of numerous cells in the centers of the lobules. In infiltrating hepatitis lymphocytes were about as numerous as polymorphonuclear leukocytes. In nodular or extensive diffuse necrotic lesions, polymorphonuclear leukocytes were dominant In every case there was degeneration of varying degree of the liver cells, ranging from simple atrophy to coagulating necrosis. In old cases there was "striking and extraordinary hypertrophy of the Kupffer cells which were increased in size, rounded, their nucleoprotoplasmic relation diminishing in favor of the latter, their phagocytic properties increasing considerably." They considered the findings constant enough to be significant but not sufficiently so to make the diagnosis of the true nature of the lesion. The absence of histiocytic nodules in the liver, the amyloid character of the typhoid hepatitis, and the subacute character of the splenitis they considered to be rough but fundamental differential elements

Forbus[249] described hepatic lesions identical with the small granulomas that occur in kidney, bone marrow, lymph nodes, and spleen. They are characteristically in the portal area of the lobule and not always large enough to be seen by the naked eye

Liver biopsy from a 65-year-old patient suffering from *Brucella suis* infection,[446] showed large numbers of round subcapsular, periportal, and mid-zone granulomatous nodules consisting of large mononuclear macrophages, mixed with lymphocytes, plasma cells, and remnants of disintegrating liver cells, with no encapsulation or necrosis Many granulomas contained various types of giant cells, some resembling Langhans' cells, others the foreign-body type.

Some light may have been thrown on the pathology of the liver in brucellosis by the work of Barker, Capps, and Allen[39] with infectious hepatitis. In fatal cases of infectious hepatitis they reported involvement of parenchymal cells, with an inflammatory exudate in the periportal areas A clinical similarity between chronic infectious hepatitis and chronic brucellosis (especially the fatigue) led them to the conclusion that the mechanism may be the same, i e attributable to liver involvement.

Cirrhosis

Cirrhosis of the liver, attributed to *Brucella* infection, has been described frequently in the German literature Lowbeer[449] translated fifteen reports dealing with cirrhosis due to or associated with *Brucella* infection Loeffler and von Albertini[443] reported biopsy of liver tissue showing granulomatous interstitial hepatitis leading to cirrhosis Hegler[322] reported postmortem findings of portal cirrhosis, splenomegaly, and ascites in 2 of 10 cases of brucellosis Diehl and Roth[176] reported 5 cases, 2 with pseudo-Banti's syndrome, 1 with esophageal varices, together with other clinical and postmortem evidence of cirrhosis. Habs'[282] case of cirrhosis was "possibly due to brucellosis" Buerger and Habs[96] found the liver often to regress after recovery Schwenckenbecher[615] and Schottmueller[616] reported 2 similar cases of hepatosplenomegaly and ultimate cirrhosis, Krohmann[418] reported atrophy of liver and hemorrhage from esophageal varices with apparent complete recovery after two years of illness. Haslhofer[317] reported a fatal case of liver involvement in a 3½-year-old child Wohlwill's[719] report was of liver involvement in a 67-

year-old woman with granulomatous changes found at autopsy. Markoff[463] reported 4 of 14 cases with granulomas of the liver leading to fibrotic healing; he assumed the first stage of *Brucella* involvement of the liver to be a serous hepatitis, the second that of necrosis and granulomas, and the third that of fibrosis and cirrhosis, stating that the first and second stages may be reversible.

In several patients similar instances of hepatic and splenic enlargement in the presence of brucellosis have been noted by the author:

In one, a woman now 69 years old, laparotomy was performed at the age of 57 because of clinical and radiographic evidence of cholecystitis. The gallbladder was apparently normal but liver was moderately enlarged and spleen markedly enlarged. No liver biopsy was done. A diagnosis of brucellosis was established following operation and *Brucella* vaccine therapy was instituted. She has never been entirely free of symptoms, the spleen becoming readily palpable on many occasions, regressing with remissions which followed reinstitution of vaccine therapy. The liver receded in size and has maintained apparently normal function. She is still quite well and able to carry on her duties as a housewife twelve years after a supposedly fatal type of cirrhosis was discovered.

Esophageal varices with rupture were reported by Diehl and Roth,[176] by Krohmann,[illegible] and by Loeffler.[442] In a 55-year-old male patient observed by the author for several years following an acute febrile attack of brucellosis, because of a chronic illness which followed, death occurred from rupture of esophageal varices.

GALLBLADDER

The gallbladder has been known to be a site of infection in many cases, the organism having been isolated from aspirated bile and from the gallbladder wall at operation. Amoss[18] reported 2 cases of involvement of this viscus in both of which a thickened posterior wall of the gallbladder was found on histologic section. Hardy and his coworkers[illegible] described chronic cholecystitis with patches of lymphocytic and plasma-cell infiltration of the stroma. The serous layer was thickened and fibrous.

Eroded mucosa, largely replaced by vascular granulation tissue and diffusely infiltrated by lymphocytes and a few neutrophiles and eosinophiles, were reported by Mettier and Kerr [478] in an [illegible] e blood culture had yielded [illegible] wall was edematous, and [illegible] hroughout the fibrous septums Two small, early granulomatous patches were found, one having a small giant cell of the foreign-body type at its center. Inspection of the gallbladder wall revealed numerous small Gram-negative rods appearing singly and in pairs, myriads of these organisms being present in the mucosal granulation tissue and throughout the wall. Cultures taken immediately after removal of the gallbladder yielded a growth of *Brucella melitensis* which was also recovered from blood.

In the case reported by Degowin and his associates [167] (p 103), postmortem examination showed edematous submucosa and muscularis, and infiltration with small round cells and polymorphonuclear leukocytes, with considerable fibroblastic proliferation

Lowbeer [416] reported no gross abnormalities in a gallbladder removed from a patient suffering from *Brucella suis* infection. Microscopic changes were striking, however, with many large round granulomas in the mucosa beneath an intact surface epithelium. They consisted of large mononuclear cells with clear pale vesicular nuclei surrounded by a peripheral zone of lymphocytes, not encapsulated and showing no necrosis Larger granulomas involving mucosa and muscle layer, with scattered lymphocytic infiltration of the surrounding wall, were found. The changes suggested the pathologic reactions to typhoid infection

GASTROINTESTINAL TRACT

Pathologic changes, none of them characteristic, in the small and large bowel have been described by Hughes [369] and by Bruce [87] and others Congestion of the entire gastrointestinal tract, most marked in the large bowel where the mucosa was edematous and sometimes inflammatory, was noted by Hughes Bruce noted proliferation and swelling of the endothelial plates

of Peyer's patches and a slight proliferation of the cellular elements of the mucous and submucous layers which were grossly almost normal in appearance. Ulcer of the bowel, mainly opposite the mesenteric attachment of some overlying Peyer's patches and almost identical to those found in typhoid fever, were found by Bousefield.[76] The ulcer margins were raised, infiltrated, with shelving sinuous edges, undermined here and there The bases were not thickened. In 2 cases the peritoneum and subperitoneal tissue alone were left while in others the muscular coat was exposed (Ulcer of the transverse colon was demonstrated radiographically in 1 of 2 of the author's patients who bled from the bowel. A third patient had had bleeding from a small ulcer just within the anus for a period of fourteen months. It healed promptly after initiation of vaccine therapy.) Hemorrhage into the bowel was reported by Sprunt and McBryde,[643] Bousefield,[76] Strachan,[654] and others. Levine and his associates[438] reported hemorrhage from ulcerative Peyer's patches.

PANCREAS

In the case reported by Degowin and his coworkers[167] (p 103), the pancreas showed small, chalky flakes on the cut surfaces, with large areas of fat necrosis, surrounded by acute and chronic inflammatory reaction and some hemorrhage. Patches of degeneration were seen throughout. Fibrous tissue was increased, and infiltrated with polymorphonuclear leukocytes and round cells. No organisms were seen on stained smear. Chronic interstitial pancreatitis with areas of infiltration, chiefly with lymphocytes and a few plasma cells and macrophages had been described by Hardy and his coworkers,[291] and by Rothenberg.[599] Pancreatic abscess has been reported.

The occasional glycosuria and hyperglycemia, with or without an attendant diabetic syndrome, seen in brucellosis (p 190), suggests pancreatitis as the possible origin Recovery in these patients, with disappearance of evidences of faulty sugar metabolism, under *Brucella* vaccine therapy may indicate the reversibility of such a process

KIDNEY

In the case reported by Degowin and his associates [167] (p. 189), kidneys showed abundant petechiae and distortion of the cortices, some of which were obliterated by yellowish-grey streaks and numerous petechiae. On the area cribrosa, numerous yellowish-grey streaks, similar to those in the calices, ascended through the pyramids and caused considerable distortion of structure. Microscopically there was evidence of diffuse nephritis, with focal areas of chronic granulomatous reaction. Many glomeruli were completely fibrosed and hyalinized, others showed crescentic scarring or were filled with erythrocytes Glomerular lesions were extensive but patchy, with many normal glomeruli Tubules showed evidence of moderate, diffuse degeneration and atrophic changes. The epithelial cells were granular and there was considerable sloughing of cytoplasm into the lumina. The nuclei contained early piknotic changes. Calcium salts were deposited in the tubular epithelium in some areas. The lumina of many tubules was filled with erythrocytes and hyaline casts. Marked distortion of the architecture was caused by profuse infiltration of the renal parenchyma with lymphocytes, plasma cells, and large mononuclears. There was complete obliteration of normal structure in some areas Inflammatory changes were particularly conspicuous in the cortex In some sections there was a chronic granulomatous reaction, characterized by small areas of necrosis surrounded by epithelioid cells The granulomatous reaction was intimately associated with small abscesses in which polymorphonuclear leukocytes as well as chronic inflammatory cells were present in some areas. There were patchy zones of interstitial fibrosis, particularly in association with the damaged glomeruli Walls of a few medium-sized arteries were moderately thickened and hyalinized (This patient had had clinical evidence of nephritis, with many erythrocytes and granular casts in the urine, as a complication of his prolonged illness with *Brucella suis* infection The kidney condition had improved, some granular hyaline casts re-

maining) No *Brucella* organisms were demonstrated in stained tissues of the kidney.

In the autopsied case reported by Parsons and Poston[520] the kidneys showed diffuse swelling and cloudiness of the tubules and a few casts in the lumina with some degeneration of the nuclei. There were no definite lesions of the glomeruli. There was an occasional area of reticulo-endothelial proliferation in the kidneys and a great many nodules of reticulo-endothelial proliferative tissue in the perinephric fat. Culture of renal tissue was positive for *Brucella*.

Forbus[229] described renal involvement as identical with the small focal granulomas found elsewhere, notably in liver and bone marrow. Meyer[452] found *Brucella* developing in the epithelial cells of Bowman's capsule and in convoluted tubules (p 98).

FALLOPIAN TUBES

Although salpingitis complicating brucellosis is of relatively frequent occurrence, there is an extreme paucity of pathologic reports. This is perhaps attributable to the unwillingness of many gynecologists to ascribe salpingitis to any etiologic agent other than the gonococcus (pp 193, 296) The author[309] has reported 24 clinical cases of salpingitis apparently of *Brucella* origin, only 1 of which was substantiated by cultural findings In none was biopsy or necropsy study possible

Amoss[16] reported a combined infection of the fallopian tubes with *Brucella* and the tubercle bacillus in a 28-year-old woman (p. 92)

Other histologic studies of *Brucella* infection of the oviducts have not been reported although it is certain that operative specimens have been available for such examination (p. 193)

OVARY

Amoss[16] mentioned oophoritis and isolated *Brucella* in pure culture from small cysts in the ovary of a 28-year-old patient In another patient hemorrhagic ovarian cysts yielded *Brucella*

Reports by Kristensen and Holm [417] and others of similar findings gave no detail of microscopic pathology of ovarian involvement.

FETUS

Maceration of an aborted 4-months-old fetus was noted by Carpenter and Boak,[116] *Brucella abortus* was isolated from the tissues Maceration of a 6-months-old fetus was reported by the author [298] in 1934, *Brucella* was recovered from lochia following the abortion. Maceration of a full-term fetus was reported by de Forest [166] in 1917; although unproved by culture, the clinical similarity in the human cases reported by de Forest with contagious abortion in cattle left little doubt as to their common etiology.

PLACENTA

Kristensen and Holm [417] reported isolation of *Brucella abortus* from exudate covering the uterine site of the placenta of a 7-months-old fetus in 1929

De Forest [166] had reported in 1917 placental changes probably attributable to *Brucella* infection, but lacking cultural proof, in several patients who had premature deliveries All showed evidence of brucellosis In one patient the placenta had entirely separated from its uterine attachment and was almost white, with a yellowish tinge The maternal surface was covered with a smooth, firm, fibrous layer of new connective tissue. There were numerous bandlike partitions of connective tissue throughout the placental structure In a subsequent delivery of the same patient the placenta showed a partial separation, was pale yellow in color, extremely friable, and quite smooth on its separated uterine surface where it was covered with a thin layer of firm connective tissue He pointed out that in animals and in man the one pathologic change present in almost all cases is a yellowish and dark-brown exudate found between the uterine mucous membrane and the chorion, varying in consistency from a mucopurulent to a tenacious gluey substance In one of his cases the umbilical cord showed a marked thickening (more than 2 inches in diameter) and a serohemorrhagic infiltration, as often found in cattle.

In a patient reported by the author,[299] spontaneous abortion occurred three times, each with subsequent foul, prolonged, profuse, bloody, and then purulent uterine discharge from which *Brucella* was isolated. In one instance the placenta was grossly necrotic in scattered areas which were filled with old bloodclot. No histologic study was made. In another, the placenta showed macroscopic areas of calcification (p. 195). *Brucella* was isolated from uterine discharge following the third abortion.

UTERUS

Although neither gross nor microscopic endometrial pathology has been reported there can be little doubt that changes occur in women who abort and whose placentas show gross changes and the more or less characteristic exudate covering the maternal aspect of the placenta. *Brucella* has been isolated from this exudate by Kristensen and Holm [417] (p. 195), from uterine discharge following abortion by the author (p. 195), and from vaginal discharge following abortion by Frei [214] Not uncommonly curettement following abortions in women suffering from brucellosis results in a laboratory report of hyperplastic endometritis alone.

EPIDIDYMIS

Simpson [627] reported recovery of *Brucella abortus* from a draining sinus tract which extended from the globus major through the scrotal wall Others [334] have reported epididymitis but no histologic studies have been described

TESTES

Sharp [613] noted the predilection of *Brucella* for the male generative tract, quoting Wainwright's estimate that mild orchitis occurs in 20 per cent of *melitensis* infections and in 4 per cent of *abortus* infections The author has seen but 6 instances among over 600 patients, most of whom were in the chronic phase Rothenberg [558] described acute interstitial orchitis and scattered areas of fibroid atrophy with vacuolar degeneration of the epithe-

lium. In the autopsy report of a case of brucellosis, *Brucella* was isolated from the testes.[526]

EYE

Brucella uveitis in the human eye was reported by Woods and Guyton,[724] who referred to Fabyan's report of 3 cases of deep keratitis in infected guinea pigs, with lymphocytic infiltration and tubercles in the cornea on histologic examination; *Brucella* was recovered from the eyes of these animals In 15 cases of uveitis attributed to brucellosis, the uveal inflammation was in no way characteristic, giving simply the picture of a recurrent iritis. In one of their patients there were definite nodules in the iris, in another questionable deep nodules, and in a third Koeppe nodules. In 3 patients the changes were limited to the choroid, the usual picture showing one or more elevated, moderately circumscribed areas of exudate with a little surrounding reaction or generalized subretinal edema. In 1 patient there was associated papilledema. In 5 patients there was generalized uveitis, progressing in 1 instance to phthisis bulbi. In 12 of the patients the process was bilateral and in 3 unilateral. In 11 of the 15 the disease was recurrent In 8 patients the uveitis appeared to be of the granulomatous type, with thickening of the iris, posterior synechiae, and heavy deposits of epithelioid cells on Descemet's membrane. In the other 7 patients the process was nongranulomatous, without nodular changes in the iris, and with small keratitic deposits of lymphocytes. In 2 patients there were associated changes in the cornea. In 1 there was only slight peripheral vascularization; in the second the pathology was that of nummular keratitis.

In the 1 patient in which the disease progressed to phthisis bulbi the eye was removed, histologic examination showing nonspecific uveitis with several conspicuous lymphoid nodules, "a picture suggestive of that of periodic ophthalmia in horses" (Fig. 9).

Woods[725] described 5 cases of *keratitis*, probably attributable to brucellosis, in which the pathologic changes were character-

In a patient reported by the author,[293] spontaneous abortion occurred three times, each with subsequent foul, prolonged, profuse, bloody, and then purulent uterine discharge from which *Brucella* was isolated. In one instance the placenta was grossly necrotic in scattered areas which were filled with old bloodclot. No histologic study was made. In another, the placenta showed macroscopic areas of calcification (p. 195). *Brucella* was isolated from uterine discharge following the third abortion.

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EPIDIDYMIS

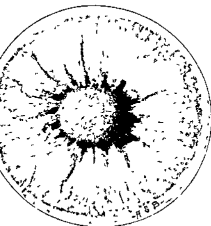
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C



D



E



Fig 9 A Lymı at the root of the iris in a case of uveitis associated with brucellosis B Lymphoid nodule near the sphincter of the iris (same case) C Photomicrograph of a lymph node in a case of chronic brucellosis D Iritis in a case of chronic brucellosis E Choroiditis in a case of chronic brucellosis (Woods, A C and Guyton, J S Role of sarcoidosis and of brucellosis in uveitis, *Arch Ophth*, 31 469, 1944)

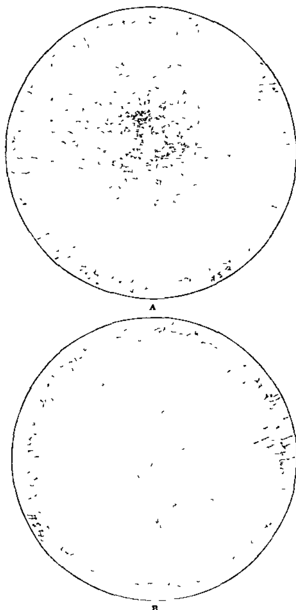


Fig 10 A Nummular keratitis complicating recurrent iritis B Nummular infiltrates in the cornea of a rabbit infected with brucellosis, produced by secondary scarification with an infected needle Six days after corneal inoculation (Courtesy of Dr A C Woods)

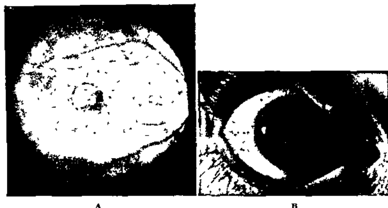
istic of nummular keratitis (Dimmer's disease). He stated that the course of keratitis in rabbits inoculated systemically with *Brucella* organisms and then having their corneae lightly scarified with a needle infected with *Brucella* organisms varied according to the virulence of the organisms used and the resistance of the rabbit. With virulent strains the infection spread throughout the eye in some normal rabbits, the corneal infiltrate increased and became confluent, iridocyclitis with exudates in the anterior chamber occurred, and the infection spread to the posterior uvea. In other rabbits there was confluence with the primary infiltrate and secondary iritis of varying intensity, followed by a gradual clearing of the eye with moderate corneal scarring and posterior residual synechiae On histologic examination these corneae showed an intact epithelium over the lesions There was some edema of the anterior uveal stroma and a moderate localized cellular infiltration, chiefly of polymorphonuclear leukocytes, in the anterior portions of the cornea beneath the epithelium. The lesions were similar to those produced by herpetic virus (Fig. 10).

Green [471] reported 4 cases of ocular brucellosis and cited 28 others from the literature (p. 246), explaining the paucity of pathologic studies by the infrequent destruction of the globe. He quoted observations [547] on 19 living guinea pigs infected with *Brucella melitensis*, some of which presented ocular lesions, stressing the great similarity to ocular tuberculosis.

At the first sign of ocular participation circumcorneal infection was noted There was slight central clouding of the cornea The iris was more or less hyperemic, the pupil was occupied by a grayish exudate. Microscopic examination of the cornea showed in cases of slight involvement the following alterations extensive desquamation of the epithelium in the central part, epithelial degeneration and formation of vacuoles in the nuclei at the periphery, formation of vacuoles in the peripheral endothelium and grave lesions in the endothelial cells, corresponding to the central clouding In several cases the corneal lesions were much more pronounced and the microscopic picture acquired a great similarity to that of syphilitic parenchymatous keratitis The iris

CENTRAL NERVOUS SYSTEM

In the case of meningo-encephalitis described clinically by Sanders,[595] Hansmann and Schenken[245] reported the following postmortem pathologic findings:



A B

Fig 11 A Hemorrhagic chorioretinitis B Keratitis and conjunctivitis (Courtesy of Dr A C Krause)

The patient was found to have died of a mycotic aneurysm of the basilar artery Liquid and clotted blood filled the subarachnoid space at the base of the brain from the optic chiasm to the brain stem, inclusive Hemorrhage completely surrounded the brain stem and was continuous with the blood clot which filled the cisterna magna, fourth ventricle, aqueduct of Sylvius, and the third ventricle The leptomeninges of the anterior and central portions of both superior surfaces of the cerebral hemispheres contained a number of greyish-white "tubercles" Most of these were found clustered along vessels. [The aneurysm and other blood vessel changes are described on page 103]

Histologic examination The pia and the arachnoid showed various degrees of thickening, due largely to an inflammatory cell infiltration and connective-tissue proliferation Inflammatory cells were largely lymphocytes and plasma cells, with a moderate number of large mononuclear and a few polymorphonuclear cells The "tubercles" showed irregular masses of hyalinized connective tissue, moderately infiltrated with chronic inflammatory cells In one area where the inflammatory cell infiltration was especially marked, necrotic tissue was present in

in the majority of cases was diffusely infiltrated, and there were numerous posterior synechiae. The ciliary body appeared to be most affected; in all cases there was infiltration of lymphoid and epithelioid cells The vitreous was often fluid. In about half the cases the lens showed definite signs of inflammatory cataract. In the anterior portion of the choroid there were found hyperemia and, here and there, foci of infiltration In the posterior portion of the uvea there was migration of the subretinal pigment with round cells and fibrin

Carpenter and Boak[114] also noted lesions of the eye produced by *Brucella* infection, similar to those produced by tuberculosis

Bilateral *papilledema* was reported in 3 of 63 cases of brucellosis, along with increased spinal fluid pressure, mononuclear pleocytosis "and evidence on which to base a diagnosis of infection of the central nervous system."[595]

Recurring *iritis* in one of the author's[303] cases complicated chronic brucellosis in a 24-year-old sailor (p 251) Death followed hemiplegia and a diffuse encephalitic encephalomalacia Post-mortem study revealed an acute and chronic form of encephalitis with lesions suggestive of *Brucella* infection. Histologic and cultural studies of the eye were not made.

Keratitis and *conjunctivitis* resembling that of luetic origin occurred in a 26-year-old woman referred to the author.[303] Cultural and biopsy study was lacking but serologic findings and clinical progress under specific therapy seemed sufficient evidence of *Brucella* infection (p 249).

Chorioretinitis, keratitis, iritis and *conjunctivitis* was seen in another of the author's patients, a 44-year-old farmer, diagnosed as ocular brucellosis by Dr A C. Krause (Fig 11) *Brucella* was isolated from the stool (p 250)

Choroiditis, uncomplicated (Fig 12), occurring in a 23-year-old woman, is described on page 247

Central–nervous-system involvement is discussed more fully in the chapter on symptomatology.

SPINAL FLUID

The spinal fluid usually shows increased pressure, pleocytosis (usually mainly lymphocytes), increased albumin, and decreased chlorides and glucose. The fluid grossly may be clear or cloudy or even frankly purulent. In the absence of definite central–nervous-system involvement Simpson [623] stated that cerebrospinal fluid may show a slight lymphocytosis and an increased sugar content, but in most cases shows no abnormalities.

BONE

Involvement of bone has been described by several authors,[139, 243, 294, 298, 302, 419, 446, 481, 599] but little on its actual pathology has been written. *Destructive changes in vertebra,* sometimes with suppuration, have been most frequently described. Reports, with radiographic and cultural evidence, of involvement of various parts of the osseous system, including skull, ribs, humerus, metacarpals, and femurs, have been rendered. Tuberculosis is sometimes closely simulated. Smith and Fabyan were quoted by Wohlwill [719] as stating that bone is destroyed from the marrow outward, from which he concluded that the bone-marrow changes which he had observed were the beginning of the osteal lesions. He described small nodules, like those found in spleen and lymph nodes, arranged in proliferal branches that extended along the dividing walls between droplets of fat.

Osteomyelitis of the femurs with operative findings resembling those of the usual pyogenic organisms and radiographic changes simulating von Recklinghausen's disease is discussed on page 219.

The tendency to new bone production overlying destructive changes seems characteristic of *Brucella* spondylitis as compared with tuberculous involvement of vertebrae.

Lowbeer [449, 450] contributed greatly to the knowledge of bone pathology in rendering reports of the first study of granulomatous changes of bone structure due to *Brucella suis* infection:

which polymorphonuclear leukocytes were noted. In another similar area, the central portion was composed of large mononuclear cells surrounded by a dense collar of lymphocytes. Newly formed blood

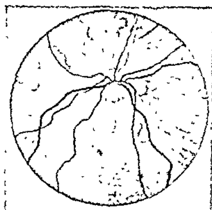


Fig 12 Choroiditis (Courtesy of Dr Algernon B Reese.)

vessels were present in many of these inflammatory cell collections. It appeared that these areas represented the various stages in the formation of a "tubercle," from necrosis to connective-tissue hyalinization. There were two small areas of softening of the brain stem The ependyma was irregular due to rounded elevations and cryptlike depressions. Proliferation of ependyma cells, especially over the elevation, was noted. In some areas complete replacement of ependyma by inflammatory cells and cellular debris was present. There was a small subependymal area of focal necrosis. Inflammatory cells were present in the perineureu of the nerve roots The central portion of one nerve funiculus was hydropic and the periphery showed condensation of nerve fibers, some of which were swollen.

Prior to death this patient's blood and spinal fluid had yielded *Brucella suis.* The patient's blood serum had agglutinated the organism isolated from the spinal fluid as well as stock strains of *Brucella* in a 1 : 160 dilution White blood count had varied from 9,000 to 15,900, with high polymorphonuclear content (87 per cent polymorphonuclear leukocytes, 10 per cent lymphoid cells, and 3 per cent large mononuclear cells) Spinal fluid had contained 300 cells, 36 per cent of which were lymphocytes

cortex There was advanced necrosis of bone marrow which was partially replaced by mononuclear exudate cells. The periosteum was *converted into a thick membrane composed* of osteoblasts and inflammatory mononuclear cells, containing osteoblasts which destroyed the cortex from the outside in many places There was complete destruction of the cortex in some places, with fragmentation in some ribs In other areas destruction of cortex took place from within. New bone trabeculae and cartilage cells were seen in some areas The similarity of the lesions in guinea pigs, hog, and man was noted In the *Brucella*-infected bones of hogs there were caseous abscess-like masses which seemed to replace an entire vertebra or the central portion of radius and ulna

JOINTS

Few histologic studies of joint pathology have been reported; most of the data available are based on clinical and radiographic studies which are discussed under symptomatology.

Destructive changes in the interarticular facets of the lower lumbar vertebrae, as demonstrated radiographically in a patient with proved *Brucella* spondylitis, has been reported [419] In another patient, with Malta-fever arthritis of the wrist, Kulowski reported a roughened and sclerotic state of the lateral half of the semilunar bone which was removed, and a similar condition in the contact surface of the scaphoid bone There was a small amount of seropurulent material in the radiocarpal joint. Histologic studies of the diseased bone or joint surfaces were not mentioned.

BONE MARROW

The more or less characteristic tubercle-like masses have been found in bone marrow as well as in spleen and in lymph nodes [229, 446, 720] They may be widespread, with involvement of large areas of medullary tissue

LYMPH NODES

Sharp [620] ascribed the process in lymph-node involvement to reticulo-endothelial hyperplasia and hyperemia, the changes being analogous to those in the spleen Tubercle-like nodules were noted to be most numerous in peri-aortic nodes [720]

A 62-year-old dentist developed a protracted *Brucella suis* infection After about twenty-seven months of a chronic illness, a gluteal abscess leading from an area of osteomyelitis of the ala of the left ilium was found Radiographs also showed a smaller area of bone destruction of the right ilium. The abscess showed "peculiar granulation tissue composed of large mononuclear cells with acidophilic cytoplasm, and showing a great tendency to necrobiosis and necrosis" There were almost no polymorphonuclear leukocytes. Occasional multinucleated giant cells resembling the bizarre giant cells seen in *Brucella* lesions, were noted

Six weeks later a second gluteal abscess from the lesion in the right ilium developed and was incised. *Brucella suis* was recovered. Simultaneously an abscess developed in the left axilla, from which the same organism was cultured Radiographs showed two destructive lesions of the left scapula

Microscopic examination of the necrotic material from the axillary and from the right gluteal abscess also showed a mononuclear cell granuloma with extensive coagulative necrosis Occasional necrotic bone sequestra were present in the exudate.

Biopsy of the right ilium showed total destruction of the cortex, with granulation tissue composed of small and large mononuclear cells and undergoing coagulative caseous necrosis toward the gluteal region, replacing the cortex and periosteum.

The peripheral osteosclerosis was pointed out as an important feature of *Brucella* osteomyelitis as demonstrated in animal lesions and in radiographs of human bone lesions

The recovered organisms were injected intraperitoneally into 7 guinea pigs Two died on the fifth and sixth day, showing a diffuse macrophagic purulent peritonitis, numerous perivascular granulomas composed of lymphocytes and monocytes in the liver, and diffuse reticulo-endothelial hyperplasia in the spleen

One guinea pig, killed seven weeks after inoculation, had shown bilateral exophthalmos for a week before, with apparent blindness, lacrymation, emaciation and enlargement of the scrotum with several fistulous openings Multiple bilateral retrobulbar abscesses filled with cheesy exudate, fusiform swelling of many ribs, from cartilage to spine, with thickened cortex and pale marrow were noted *Brucella suis* was recovered from retrobulbar and testicular abscesses.

The thickened ribs showed periosteal osteophytes surrounding the

of fatal brucellosis)[475] came to autopsy, after repeated exacerbations of an acute illness during which there was fever, malaise, weakness, anorexia, chilly sensation, diarrhea, and slight cough. [illegible] athy, biopsy of a supracla- [illegible] adenitis with necrotic foci, [illegible] tuberculosis" *Brucella* was grown from the nodes. In biopsies of lymph nodes in all 4 cases the histopathologic changes were identical with those found in Hodgkin's disease: (1) complete destruction of the original architecture of the lymph nodes, (2) pronounced eosinophilia, (3) focal scarring, (4) production of large, pale mononuclear cells, and (5) production of giant cells of the Dorothy Reed type (Fig 13). The authors considered it possible that this type of histopathologic reaction may be caused by *Brucella* infection and warned that simple biopsy of a lymph node is not a sufficient basis on which to diagnose Hodgkin's disease.

Autopsy findings in the case in which death occurred were:

(1) Generalized lymphadenopathy, especially of the retroperitoneal nodes and at the liver hilum, (2) yellow fluid in all serous cavities, (3) old and recent fibrous and fibrinous adhesions of the lungs with multiple small, circumscribed, pale, opaque nodules in the cut surfaces, (4) similar nodules in liver, spleen, and bone marrow, (5) marked enlargement of the spleen, (6) destruction of the left adrenal gland by encroachment of the tremendously enlarged retroperitoneal lymph nodes Microscopic study of all nodes showed large areas of necrosis made up of homogeneous eosinophilic material which contained little or none of the original cellular elements

In discussing the findings in these 4 cases, Kracke[413] commented on the possibly far-reaching importance of the work in explaining an etiologic relationship between *Brucella* infection and some types of Hodgkin's disease Forbus[228] stated that it is not at all *impossible that brucellosis and Hodgkin's disease represent* merely different phases or variants of the basic reaction to one or the same injuring agent The extraordinary similarity between the reaction of human tissues to *Brucella* and to that

Hemorrhage in abdominal lymph nodes[618] and a semifluid purulent content in the mesenteric nodes[207] have been reported.

Bloomfield[62] reviewed the literature, finding frequent reports of clinically noteworthy enlargement of superficial lymph nodes but few reports of biopsies and cultures. The similarity to Hodgkin's disease was noted—prolonged fever, palpable spleen, palpable lymph nodes and eosinophilia, plus the occasionally similar cellular arrangement.

Lymph nodes in the pelvis, around the aorta, and near the celiac axis were moderately enlarged and red, with hemorrhages partially obliterating the architecture in one case.[167] Microscopically there was marked hyperplasia of the germinal centers, with hyperplasia of the endothelial elements and dilation of sinusoids which were filled with erythrocytes and large mononuclear cells. No areas of necrosis were noted. The organism was not seen in stained sections of lymph nodes but was recovered from guinea pigs inoculated with macerated lymph-node tissue.

In one of the author's cases the ileocecal lymph nodes were found markedly inflamed at laparotomy performed because of the suspicion of a neglected surgical condition. Symptoms had simulated appendicitis (p. 183). The surgeon removed no tissue for histologic and cultural study.

Cultural and histologic study in the author's cases was handicapped by lack of facilities Among 31 instances of lymphadenopathy, culture alone was attempted in 6, all with negative results. Distribution of lymphadenopathy was widespread—anterior and posterior cervical, submaxillary, axillary, inguinal, and mesenteric. The presumed relationship to *Brucella* infection in many cases was based on other laboratory and clinical evidence of brucellosis, upon regression of glandular involvement with clinical improvement, and recurrence with relapse

Similarity to Hodgkin's Disease

Parsons and Poston[526] described 4 cases of chronic brucellosis which presented striking clinical and histologic similarity to Hodgkin's disease One case (originally reported as a rare instance

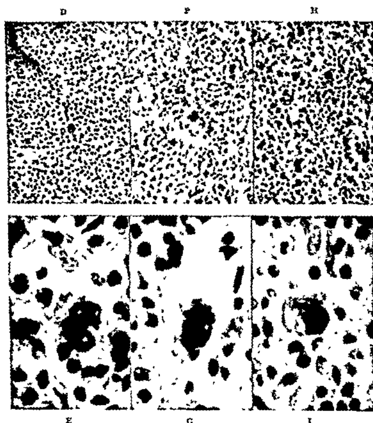


Fig. 13. D Section of lymph node diagnosed as Hodgkin's disease, from which *Brucella* was grown (×150)

E High power study of D (Hematoxylin and eosin ×500)

F Biopsy of lymph node diagnosed Hodgkin's disease, from which *Brucella* was grown. (×150)

G One of the large cells in F (×500)

H Section of lymph node from cervical region, showing Dorothy Reed cells *Brucella* was grown from this node (×150)

I High power study of H (×500)

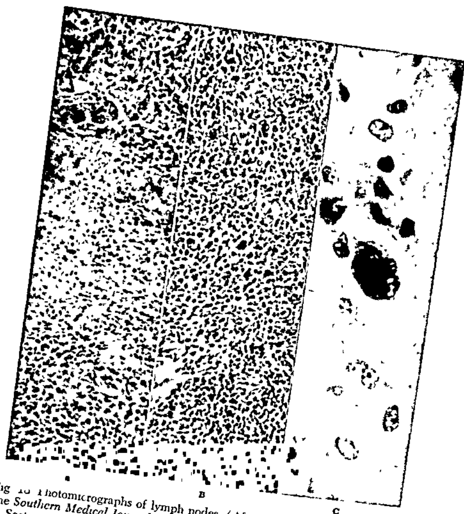
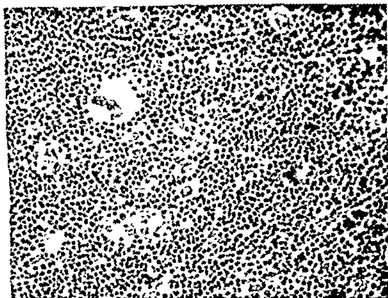


Fig 16 Photomicrographs of lymph nodes (After Parsons and Poston Courtesy of the *Southern Medical Journal*.)

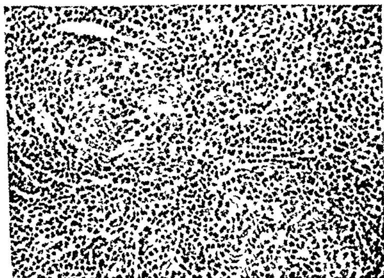
A Section of lymph node biopsy one year before death, showing non-specific necrosis (Hematoxylin and eosin ×150)

B Section of retroperitoneal lymph node removed at autopsy Large numbers of eosinophils, diffuse fibrosis and many Dorothy Reed cells (Hematoxylin and eosin ×150)

C High power view of B



A



B

Fig. 34. A and B. Lymph node biopsy of patient with chronic brucellosis. Differential diagnosis between *Brucella* infection and Hodgkin's disease could not be made from these sections. Death from Hodgkin's disease occurred four years later.

agent, whatever it may be, which is responsible for Hodgkin's disease had been confirmed by his own studies of the materials upon which the report was based and other cases of Hodgkin's disease.

In 1940 Poston and Parsons[319] recorded the isolation of *Brucella melitensis* from the blood or lymph nodes in 14 consecutive cases of Hodgkin's disease, whereas in the control series of 67, cultures of lymph nodes obtained from individuals without Hodgkin's disease, only one yielded *Brucella*. Poston[318] discussed recovery of *Brucella melitensis* from lymph nodes of 10 of 19 patients with Hodgkin's disease.

Wise[318] studied 11 patients with Hodgkin's disease, isolating *Brucella melitensis* or *suis* from the blood of 10 and from the lymph nodes of 6. In a control series of 58 patients without Hodgkin's disease *Brucella melitensis* was isolated but once. He stated that positive blood cultures were obtained with greater frequency when Hodgkin's disease was actively progressive than when it was subacute or temporarily arrested. He felt that his study did not establish an etiologic relationship between *Brucella melitensis* and Hodgkin's disease but that the clinical course of the latter was directly influenced by the coexisting *Brucella melitensis* infection.

In 2 of the author's cases, brucellosis and Hodgkin's disease coexisted. Cultural study before death was negative for *Brucella* but lymph-node biopsy was more suggestive of *Brucella* infection than of Hodgkin's disease (Klemperer) (Fig. 14). Cultural examination of tissues was not carried out at autopsy. In the other patient *Brucella abortus* vaccine therapy had been followed by marked regression of mediastinal and abdominal tumor masses on each of several occasions, coincident with rise in the phagocytic index and desensitization to *Brucella*. In the first patient there had been no response to the same treatment.

In a later personal communication Forbus[219] stated

> With regard to the relationship between Hodgkin's disease and *Brucella* I believe that the matter is still in a very uncertain position

back. Physical examination was otherwise negative Routine laboratory studies were all negative except for slight leukopenia with relative lymphocytosis. His opsonocytophagic reaction showed a high degree of resistance to *Brucella* infection Intradermal reaction was marked to B.A C *abortus* and very marked to all three species of killed organisms The intradermal reactions to the *Brucella* vaccines so very closely simulated the nonsuppurating skin lesions as to be indistinguishable from them in color, shape, and gross texture As the skin reactions began to subside there was notable improvement in his subjective symptoms *The skin lesions slowly faded, giving added weight to the* likelihood that they were a manifestation of brucellosis Later, after mild recurrence of illness, with reappearance of a few skin lesions administration of streptomycin and sulfadiazine was followed by complete resolution of all symptoms, including the skin lesions.

One of the lesions had been excised for histologic and bacteriologic study These slides were reviewed by Dr. Paul Klemperer as follows

"The slide shows a fragment of skin, in the center of which there is a relatively sharply defined inflammatory lesion. The surface epidermis is slightly hypertrophic with moderate hyperkeratosis, which is even less conspicuous than that in the adjacent portion The deeper layers of the epidermis show some intracellular edema and cell enlargement Between the cells there are occasional multinucleated leukocytes The papillary layer shows edema and infiltration with polymorphonuclear leukocytes and lymphocytes The capillaries are frequently widened and show conspicuous swollen endothelial cells Around smaller arterioles there is a rather dense infiltration with polymorphonuclear leukocytes and lymphocytes, and infiltration becomes much more pronounced in the deeper cutis. Here, a very conspicuous proliferation of adventitia cells with histiocytic differentiation can be seen, especially around small veins This proliferation is associated with polymorphonuclear leukocytic and lymphocytic infiltration There are also small aggregations of polymorphonuclear leukocytes between the thick connective-tissue bundles impressing one as micro-abscesses. The inflammatory reaction fades in the deepest layers of the corium

"From the foregoing description of the histologic findings one can say that we are dealing with a circumscribed papular inflammatory skin lesion The question is whether the histology is in any way characteristic I would hesitate to designate it as such, but I would like to call attention to the fact that the perivascular histiocytic prolifera-

Certainly in all of our experimental studies we have not been able to produce in any of a variety of experimental animals a disease which is like Hodgkin's disease, other than, of course, the basic reaction in both dogs and hogs. . . . In none of the animals was there a typical picture of a Hodgkin's lesion. We have had to conclude, therefore, from our studies that we have been able to do nothing more than produce the basic reaction type, that is, a reticulo-endothelial reaction by means of the strains of *Brucella* that we got from our cases of Hodgkin's disease.

SKIN

Skin lesions of various types have been described clinically (p. 255) but with extremely few histologic or cultural studies

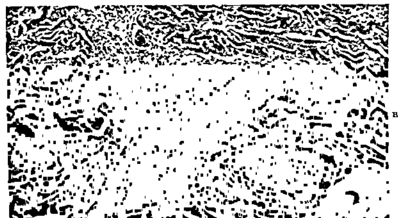
Flanchik and Freyfeld [221] described an ulcerative dermatitis following accidental skin inoculation with *Brucella abortus* in a laboratory worker. One lesion was described as a round ulceration, the base covered with weak granulations and exuding a serohemorrhagic fluid from which a pure culture of *Brucella abortus* was recovered. Zeman [726] described a case of Bang's disease with necrotic cutaneous lesions, also without biopsy.

Mettier and Kerr [478] reported histologic examination of a biopsy specimen from a lesion in a patient having a generalized maculopapular, erythematous rash Vascular hyperemia and slight perivascular infiltration of lymphocytes, consistent with the diagnosis of subacute inflammation of the skin, were found. Blood culture was positive for *Brucella melitensis* but no organisms were isolated from the biopsy specimen.

Biopsy of a skin lesion in one of the author's patients may throw some light on the type of skin pathology caused by brucellosis

A 43-year-old American male living in Cuba was referred in August, 1947, by Dr Carlos A Fernandez, because of a persistently recurring generalized skin eruption which had begun in 1944, and because of "lack of strength and coordination" which had persisted since a febrile illness thought to be pneumonia in 1945 The skin lesions were orange-red papules varying in size from 0 5 to 2 5 cm in diameter, some tender and ultimately exuding pus, others subsiding without suppuration They were generalized except for the face, more profuse on legs and





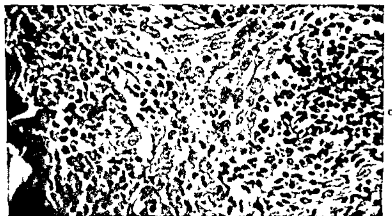


Fig 15 A, B, C Biopsy of papulo-pustular skin lesion (description page 139)

tion is rather unusual, especially since these perivascular lesions assume the character of small perivascular granulomas The size of the histiocytes and their conspicuous nucleoli is also somewhat unusual, although by no means specific I only mention that because we find in brucellosis sometimes similar histiocytic proliferations in enlarged lymph nodes. Of course one has to question whether this histologic feature is due to direct action of the organism or rather the result of a peculiar reactivity of the host as it occurs in chronic bacterial infections" (Fig. 15 *a, b, c*). *Brucella* was not recovered on culture of part of the same lesion.

A persistently necrotic skin area produced by heat-killed *Brucella abortus* organisms used as an intradermal test was excised because it failed to heal after four months The microscopic findings were similar to those described by Klemperer in the naturally occurring lesion described above (Fig. 15 *d, e, f*). They were:

Sections of the skin lesion show a chronic granulomatous process with caseo-tuberculoid necrosis Histologically the lesion consists of a large granuloma surrounded by a conglomeration of small granulomas The large granulomatous process consists of a central necrotic area filled with puriform material and disintegrating polynuclear leukocytes This is surrounded by a wide zone of epitheloid cells intermixed with fibroblasts and containing numerous multinucleated giant cells both of the foreign body type as well as some closely resembling the Langhans' type. Next to this zone is a mantle of lymphocytes of varying depth The large central granulomatous mass ulcerates through the skin and extends deeply into the hypodermis Adjoining this larger granuloma and extending on both sides of it as well as to the deeper layers are conglomerations of subdermal small granulomas composed of a central core of epitheloid cells and fibroblasts surrounded by a zone of lymphocytes and containing a number of multinucleated giant cells similar to those described above

While histologically the granulomatous process somewhat resembles tuberculosis the type of necrosis differs from true caseation The necrotic centre consists essentially of a homogenous hyalin necrotic material and is infiltrated by polynuclear leukocytes in various stages of disintegration





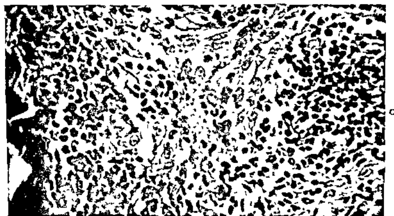
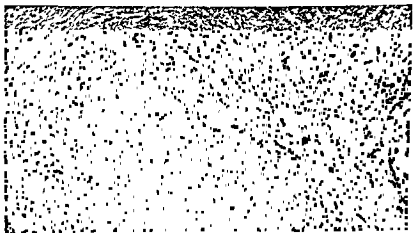


Fig 15 A, B, C Biopsy of papulo-pustular skin lesion (description page 139)


D





No bacteria were demonstrated in sections stained with Giemsa's stain

If cultural and histologic investigation of biopsy material is carried on concurrently in properly equipped laboratories, much should be added to present knowledge of the pathology of this disease. Failure on the part of surgeons, internists, bacteriologists, and pathologists to believe that *Brucella* infection is an important cause of illness has contributed largely to the paucity of information

Chapter V

SYMPTOMATOLOGY

No disease, not excepting syphilis and tuberculosis, is more protean in its manifestations (Walter M Simpson, *Tice's Practice of Medicine*, W F Prior Co)

Incubation Period

BRUCE[82] stated that it is impossible to define the incubation period within narrow limits but he believed that it ranged from a few to twenty or thirty days Cases occurred in epidemic proportions in a regiment six days after it arrived in Malta He quoted instances in which the disease became apparent in persons on their arrival in England fourteen to seventeen days after leaving Malta

Bassett-Smith[illegible] called attention to the long delay in the appearance of symptoms in some patients, stating that it may be two months or more

Hardy, Frant, and Kroll[illegible] investigated the probable incubation period in 17 persons who were thought to have become infected by raw cow's milk during single out-of-town visits of six days to eleven weeks duration Wide variations of from one week to four months were found To explain them they mentioned variations in virulence of the three varieties of *Brucella*, the different modes of inoculation, and the probable variation in the dosage

Beattie and Rice[illegible] reported a milk-borne epidemic of acute brucellosis due to the porcine variety, 30 patients contracted the

disease, 27 of whom used raw milk from one dairy. All the cases occurred within a period of three months, the last case thirteen days after the sale of milk from the suspected dairy was stopped.

In the study[345] of 17 cases of acute brucellosis among laboratory workers exposed to *Brucella suis* and *Brucella melitensis*, the incubation period was thought to have been at least four weeks in 1 case because there had been no known opportunity for exposure for that length of time immediately preceding the onset of illness In the other cases no definite conclusions could be drawn since all had been in almost daily contact with the infecting organism for three to thirteen months before they became ill.

A definite history of exposure may be of value The known or suspected exposure may not have been the first. Latent or subclinical infection may have existed for months or years Most estimates of incubation period are based on the assumption that the individual is well until a certain date and that, as with scarlet fever, an acute illness is ushered in with more or less typical prodromes. This is often true in epidemic outbreaks of acute brucellosis, but it does not apply to the chronic illness. If the actual onset cannot be determined with any degree of accuracy, because of its insidiousness, then the incubation period must be said to be undeterminable.

Mode of Onset

The onset of the acute illness may be abrupt or gradual and attended by few or many extremely varied symptoms of any degree of severity Illustrative examples are as follows.

A 24-year-old farmhand had been under observation for a period of several weeks to determine the nature of his afebrile chronic illness of two years duration He complained of rather more than usually severe headache on one consultation during the second month of his observation Temperature, previously within normal range, was found to be 99.4° F by mouth That afternoon temperature was 100.2° F Blood-agglutination reaction with *Brucella abortus* was positive in a 1:2500 dilution Next day temperature was 101° F, four days later

reaching an afternoon peak of 101.6° F., and two days later 103° F. Thereafter for ten weeks, fever ranged from 100 to 101° F. each morning to 104 or 105° F. each afternoon Headache, sweats, malaise, epistaxis, chest pain, orchitis, cough, and constipation of varying severity constituted his chief symptoms. Prostration was extreme He had been unwilling to remain in bed during the first two weeks of the acute illness, so gradual was the onset of the more severe symptoms.

A 50-year-old merchant felt well until a sudden chill occurred one afternoon Temperature was 103° F. Except for weakness and sweating he had virtually no complaints throughout the three-week course of his febrile illness. Because of the nature of the onset his attending physician had made a diagnosis of lobar pneumonia which was only disproved by continued absence of chest signs or symptoms and a blood-agglutination reaction with *Brucella* in a titer of 1:320.

Grippelike onset, with headache, backache, and malaise, was noted in 20 of 31 acute cases of brucellosis. Joint pain and swelling suggesting rheumatic fever, of rapid onset, were the first noticeable manifestations of acute brucellosis in 3 cases. Chill, cough with blood-stained sputum, pleuritic chest pain, and febrile reaction, giving a clinical and radiographic picture of the usual pneumococcic pneumonia, ushered in the acute illness in 1 patient admitted to the author's wards in a naval hospital

Hardy and his coworkers [285] attempted to estimate the interval from the appearance of the first symptom to the time of the first medical consultation, or to the time when the patient became bedfast, calling this the period of onset. Among 230 cases the duration of this period was less than one week in 27 (12 per cent), one-half of these showed abrupt onset. In 38 cases (17 per cent) it was one week, in 55 cases (24 per cent) ten days to two weeks, in 61 cases (26 per cent) three weeks to one month; in 19 cases (8 per cent) six weeks, in 30 cases (13 per cent) two months or longer. The symptomatology was highly varied during this period of onset.

The insidiousness of the onset of symptoms in the great majority of chronic cases renders it as difficult to compute the date of infection as it is in tuberculosis.

CLASSIFICATION

Hughes[369] grouped cases occurring at Malta in four main categories: (1) malignant, (2) undulatory, (3) intermittent, and (4) irregular and mixed types

The "ambulant type" of illness was noted by Shaw[624] among persons in whom symptoms were absent or consisted only of a few days of slight fever He examined the blood of 525 Maltese dockyard employees, all of whom were working full time, for agglutinins Of the 15 per cent showing significant agglutinins the 22 whose titers were the highest were carefully studied Ten of these yielded positive cultures.

Simpson[630] described five types of the disease as seen largely in the mid-Western United States.

1 Intermittent, usually with subacute course, intermittent fever, and a usual duration of three to four months
2 Ambulatory, with less severe symptoms than in the intermittent type, usually with weakness and mild fever, often confused with influenza, and comprising the majority of all cases.
3 Undulatory, characterized by relapses, usually decreasing in severity, often with physical and mental deterioration and comprising about 15 per cent of the cases seen in the United States.
4 Malignant, of sudden onset, acute course with extreme hyperpyrexia, usually with a fatal termination, usually of one to three weeks duration, and comprising about 2 per cent of the cases reported in the United States
5 Subclinical, representing infection in persons in the absence of clinical symptoms and signs of the disease.

Hardy and his coworkers[295] made a painstaking analysis of 375 cases of *abortus* and *suis* infection in Iowa About 25 per cent were "ambulatory," most were classed as "intermittent," few showed the "undulatory" pattern of fever (although almost 15 per cent suffered relapses), the "malignant" type constituted less than 1 per cent More than 50 per cent were acutely ill at some time, with fever and prostration The classification of these cases

as acute or chronic, or as intermittent, ambulatory, malignant, or mixed types would depend largely on the phase of the illness during which the patient was seen, upon the stress placed upon past illness referable to brucellosis, and upon the period of observation.

Classification as acute or chronic seems preferable, although the two often merge or alternate with each other.

THE ACUTE ILLNESS

Symptomatology is so varied that no concise description is possible.

The severity and duration of the acute infection vary greatly Many individuals suffer one single attack and apparently recover completely, or this attack may be followed by remission and one or many subsequent recurrences over an indefinite number of years The acute phase may be preceded by weeks, months, or years of the chronic phase The patient who has repeated relapses does not necessarily convalesce following the acute attack, he may have only partial remission, with infection still present but temporarily checked by his own immune processes Remissions often are not complete, fatigue, slight fever, and vague symptoms may persist throughout the intervals between relapses, or continue indefinitely as a chronic illness

Grippe may be simulated by acute brucellosis in its milder manifestations The patient may complain only of headache, backache, and general malaise. There may or may not be cough, which may be nonproductive or productive of a frothy mucus or purulent sputum Fever may be that typical of grippe, the only clue to the diagnosis being its persistence beyond the stage where grippe usually terminates The backache and other joint and muscle pains are usually more severe than those experienced with grippe Various patients have remarked that, if this was grippe, it was not exactly like any attack previously experienced The height of fever and its pattern and duration vary widely Prostration is not necessarily proportionate to the febrile reaction Three patients elected to come to the office with temperatures ranging

from 103 to 105° F Others may be greatly prostrated with fevers no higher than 102° F

Chills may accompany each rise in temperature or may be absent. Commonly there are profuse *sweats* that may be indistinguishable from the sweats of grippe, influenza, malaria, typhoid, or other acute illnesses. Hardy[295] noted sweating in 84 per cent of cases, but not in the very mild cases with low-grade fever nor in the malignant ones with high, sustained fever The patient who has had previous acute phases which were recognized as brucellosis, may call the physician's attention to the characteristic, unpleasant odor of the sweat. A nurse who had suffered innumerable relapses over a period of seven years, with temperature ranging as high as 107 2° F., felt that she could distinguish in herself a relapse of brucellosis from an attack of grippe by the odor of the perspiration. An interne attending a patient during the attack of acute brucellosis frequently remarked that the odor of the perspiration was "peculiar," before it occurred to him to suspect brucellosis. Casey[129] described it as a "mousey" odor It may also be described as "rancid," "ammoniacal," or resembling that of menstrual blood Unlike the usual situation as regards body odor, the patient is often keenly conscious of the odor whereas the attendant or associates may be unaware of it.

Pain may be complained of, usually as generalized aching, but involving any part of the body Lumbar, dorsal, or cervical localization is common Headache is frequent, especially with febrile reactions Joint pain is frequent and of variable severity (p 201) Abdominal pain, of varying localization, is a variable complaint but often severe.

Loss of weight occurs in the great majority In only 10 per cent of the cases studied by Hardy was there no apparent loss Emaciation may be extreme.

Pallor may be fairly characteristic, irrespective of anemia.

Symptomatology of the acute illness may show tremendous variations Any of the myriad signs and symptoms may be combined in varying degrees of severity. The more important of them are described under "Regional Symptomatology."

Duration of the acute illness is variable; not uncommonly the whole attack lasts but a few days, although in the more severe form there may be a daily rise of temperature for periods of twelve weeks or more. Those protracted, acute illnesses often closely resemble typhoid fever, even to a "rose-spot"-like rash. Neurologic involvement may appear late in the illness, as indeed may any of the symptoms or syndromes to be discussed.

The course of the untreated or refractory acute illness is unpredictable. In patients infected with *Brucella suis* the illness was not discernibly different from that of patients infected with *Brucella melitensis*, in 17 acute laboratory infections.[345] In some cases the initial attack was most severe; in others subsequent attacks were more prostrating and prolonged One episode occurred in 5 patients, two episodes occurred in 9, three episodes in 2, and five episodes in 1 patient. Physical activity often was followed by relapse. It was considered possible that attempts to immunize these persons in advance may have altered the course of the illness. In general but not uniformly, *abortus* infections are less severe.

Recovery from the acute attack usually is gradual, the fever slowly subsides, and subjective and objective improvement follows gradually in the usual illness. Relapse may occur at any time, even when the patient seems almost to have recovered.

THE CHRONIC ILLNESS

The chronic illness may begin as such or may follow an acute attack. The history often is not clear-cut, the preceding acute illness having been diagnosed as influenza, malaria, rheumatic fever, or other condition, or there may have been no acute illness

Temperatures of 99 to 99.6° F. or higher may be found in the late afternoon only and perhaps for only an hour or two, or there may be no fever.* Most of these patients have recurrent symptoms, but some remain ill month after month. Many are able to continue their occupations *Fatigue of varying degree is practi-*

* Unless mouth temperatures are taken for five-minute periods these low-grade fevers will not be detected.

cally the only subjective symptom common to all cases of brucellosis. Additional symptoms and syndromes that may occur, in any combination, will be discussed more fully under "Regional Symptomatology"

Beatty [48] stated: "In many cases of proved chronic undulant fever no acute stage can be recognized from the history Evidently some of these run a somewhat chronic course in the beginning And again probably many [others] have had the infection for years, dating from childhood or early adulthood when clinical history is not well recalled, and from time to time receive massive reinfection but are the natural exacerbations and remissions of the disease"

Angle and Algie [20] aptly said: "There is no group of symptoms which are characteristic of chronic brucellosis; in fact, the variety and vagueness of the complaints are features of the disease"

Robinson and Evans [530] described the chronic illness as follows·

> In severity it varies from a very mild form to a prolonged progressive disease which may end fatally Chronic brucellosis may appear as a sequel to an acute attack or the onset may be insidious The patient may be aware of no illness other than mild symptoms of weakness, nervousness, exhaustion on slight effort, suffocating sensation, palpitation, insomnia, depression, irritability or sense of impending disaster Fever is usually present in low degree, it may be absent for weeks or months, when the patient may suffer from any or all the mentioned symptoms A common feature of chronic brucellosis is the lack of abnormalities to be found in physical examination . When the mild symptoms described occur in a patient with no apparent physical abnormality, the picture represents that classified as psychoneurosis One of us pointed out in an earlier paper that in many cases of chronic brucellosis a diagnosis of neurasthenia is made In general our cases illustrate the chief features of chronic brucellosis—weakness, low-grade fever, and a lack of objective signs of disease.

The patient with the chronic illness, even though febrile and with demonstrable pathology and positive cultural findings, often presents the picture of radiant health The expression "You feel

so sick but you look so well" is frequently used by family, friends, and physicians, with the implication that the patient is a psychoneurotic if not a malingerer. On the other hand, many patients reflect their misery in their appearance.

A Navy nurse seeking retirement expressed the frustration she felt at being told repeatedly that her complaints of fatigue, generalized pain, and low-grade fever were of psychic origin and that it was "up to her to realize that she did not have brucellosis." In her rebuttal to the decision of a Board of Medical Survey to refuse retirement she wrote: "Permit me, as the person most interested, to invite attention to the fact that anyone without personal experience with undulant fever cannot possibly successfully gauge either the mental fears or the physical depression assailing one suffering from undulant fever, as the inevitable daily rise of temperature takes place to a degree directly in proportion to the amount of activity accomplished." Cognizance by Navy Medical Officers was taken of the viewpoint expressed by the patient in a subsequent opinion which stated. "The symptoms appear out of proportion to the objective findings but this is a common occurrence in this disease."

In some patients there is noted regularly recurrent prostration as even low-grade fever develops each day, regardless of activity. In others in whom there is no temperature elevation whatever the exhaustion may be equally as profound.

A physician suffering from chronic brucellosis made the following distinction concerning the fatigue of psychoneurosis and that of brucellosis "If fatigue is due to neurosis, continuation of graded exercise should result in improvement and greater tolerance, in chronic brucellosis if one continues to exercise in spite of fatigue, then exhaustion, tremor, lack of muscular control and coordination develops" He pointed out that the muscular sensations of the patient who is incapable of exercise is exactly similar to that of the well person who has exercised too much

There are patients with minimal symptoms who might be called sick or well, depending upon the temperament of the patient and the viewpoint of the physician The individual with a mild infec-

tion, or with a nearly adequate resistance to infection, may suffer nothing more severe than headache, backache, and fatigue which may be felt for only a part of each day, wearing off through the morning or occurring at the end of the day, or loss of weight, vague muscle and joint pains, and perhaps a degree of despondency. If he is of a phlegmatic nature he may make little complaint, especially since these symptoms are apt to appear and disappear spontaneously. If he consults a physician who does not recognize so mild a form of brucellosis, he is likely to be told that there is nothing organically wrong with him. Since the average physical and laboratory examination usually reveals nothing, he may seek no further help, especially because there are likely to be periods of relatively good health. If the patient is of the opposite temperament he may seek help from one physician after another until he finds one who recognizes the cause of his illness or convinces him that he is suffering from psychoneurosis rather than brucellosis By then the psychogenic component actually may be great.

The differential diagnosis between chronic brucellosis and psychoneurosis may be difficult It is discussed at length in the chapters on diagnosis and psychologic studies.

BRUCELLOSIS IN CHILDHOOD

The acute illness in childhood may present a general picture that is much the same as that seen in adults Onset may be gradual or sudden Fever, with or without gastroenteritis, symptoms of upper respiratory infection, atypical rashes, vomiting, constipation or diarrhea, abdominal distention, sweats, delirium, nuchal rigidity, localized or generalized adenitis, and a multitude of other symptoms may be encountered in almost any combination Central nervous system involvement may occur [510] Not infrequently the acute exanthematous diseases, such as measles or pertussis, may be closely followed by prolonged undiagnosed fever, persisting long after convalescence should have been established, ultimately leading to consideration of brucellosis, previ-

ously existing as a latent infection and flared up by the intercurrent illness.

Paterson and Hardwick[527] stressed the more abrupt onset in children, although this has not been noted by most other observers. In 5 of 8 cases in children between the ages of 6 and 14½, the onset was with signs of infection of the nasopharynx, leading to the diagnosis of a cold or influenza. They reported persistence of fever in all, sweating in 2 patients, marked prostration in 1, splenomegaly in 1, anemia with relative lymphocytosis in 2, and blood-agglutination reactions in titers of 1:500 or higher in all. (The author has so often seen brucellosis follow other acute infectious diseases such as measles—apparently because of the lowering of general resistance—as to suggest the possibility that the early symptoms in some of the patients reported on by Paterson and Hardwick may indeed have been due to colds or influenza, followed by exacerbation of previously latent or subclinical brucellosis.)

Hagebusch and Frei[285] described brucellosis in 182 children between the ages of 3 days and 16 years, of whom 95 per cent were under the age of 6. Of these 182 cases, 6 were acute illnesses and 176 chronic illnesses. There were very few abnormal physical findings. An occasional child had an enlarged liver or spleen, a somewhat greater number had definite but poorly localized abdominal tenderness, a few had generalized lymphadenopathy. A reddened throat without subjective symptoms was rather common. Six patients were followed for seven years and 2 for ten years. They were well and healthy up to the time of the acute attack and none had completely recovered, still having fever and other signs of active disease. In two family groups observed for a period of two years, all exposed to infection from the milk of an infected herd, all 10 persons developed mild illnesses characterized by aching and fever soon after exposure, all had positive blood-agglutination reactions and skin tests, and all, except 1 adult in one family and 1 child in the other, promptly recovered. These 2 developed chronic brucellosis.

The chronic illness in childhood is commonly manifested by the

so-called run-down state wherein the child, previously robust, becomes languid, pale, irritable, fails to gain weight, tires easily, and may exhibit low-grade or no fever. This syndrome, or any of the individual symptoms, may occur at intervals with fairly normal periods of remission, or it may continue without remission. If temperature is recorded accurately over a period of days, a low-grade fever, commonly from 99 2 to 99 6° F., usually will be found in the afternoon or evening although it may not occur daily. Blood study often reveals some degree of anemia, leukopenia, and often accompanied by a marked relative lymphocytosis Urine may show from a few to many leukocytes, commonly a trace of albumin and a few granular casts Glycosuria is not infrequently found. Failure to gain weight and fatigue are likely to be the outstanding symptoms. There often is a history of pyelitis, of undetermined etiology.

Duration of the chronic illness in untreated cases may be indefinite

In *infancy* symptomatology is more obscure Repeated gastrointestinal upsets may occur. Failure to gain weight normally may be the only symptom to call attention to the possibility of brucellosis The infant may be simply pallid and sickly, with constant low-grade fever or periodic bouts of fever for which no cause may be assignable Pyelitis apparently is a not infrequent complication, and may be the only manifestation, as in older children Sustained high fever, with few physical signs, may constitute the major clinical manifestations of the acute illness.

The onset of childhood brucellosis may have been at birth or shortly after birth Although laboratory evidence was lacking, highly suggestive symptoms of brucellosis were noted in 2 successive babies born to an infected mother Both were normal and healthy at birth but pallor, listlessness, moderate fever, and failure to gain weight became evident within a few weeks and persisted for several months There was no other adequate explanation for their illnesses Ultimately both infants recovered.

Hagebusch and Frei [485] reported 26 cases in infancy, with clinical symptoms (p 42) and positive tests before they had had any

food other than mother's milk. In 4 there were relatively severe symptoms before nursing and before taking any food other than dried or evaporated milk.

Symptoms in infancy and older childhood are discussed more fully under "Regional Symptomatology."

WEAKNESS AND FATIGUE

Physical weakness and easy fatigability are among the outstanding complaints in the vast majority of patients in both the acute and the chronic illness. Rarely does the patient fail to mention it in history-giving or to stress it if the symptom is elicited on questioning. *Although many criteria have been suggested for the distinction between the weakness and fatigue of brucellosis and that so commonly found in the neuroses, there is no characteristic pattern* The fatigue, with or without definite prostration, may not be constant but may occur at any time of day The patient with proved brucellosis may find that he can attend to his daily duties for the first several hours of each day and that he then rapidly tires or, apparently just as frequently, the complaint of fatigue involves the morning hours, wearing off through the day Whether or not an emotional state enters into the causation of fatigue in some or in all of these patients with chronic brucellosis is a matter of speculation Certainly in the frankly neurotic individual the physician is entitled to suspect that the emotions are at least a contributing factor In those with no discoverable neurotic reactions to illness or to life situations, fatigue and weakness seem to occur with equal severity and frequency.

Allan[10] stated that there are four pathognomonic features of weakness and fatigue arising from a nervous state, as follows: (1) weakness greater in the morning, wearing off during the day, (2) variability from day to day without change in activity to account for the difference, (3) immediate benefit from the use of slow-acting medication such as thyroid, vitamins, liver extracts, iron, and digitalis, (4) immediate relapse on omission of customary treatment with these drugs

The reliability of the first two criteria is open to serious question. The latter points are undoubtedly helpful in making the distinction However, the patient with a chronic physical illness may claim benefit out of all proportion to the therapy because of hope that a frustrating experience has finally been ended by the magic which patients are likely to ascribe to their chosen physicians The improvement in these patients would be expected to be short-lived, or, if prolonged, to be based on the known psychogenic effect of taking medication which they believe will be of help Such a reaction does not rule out concomitant physical illness

Allan listed among "other features of probable importance" complaints of more than three years duration without any physical disorder to account for them Brucellosis is, of course, one of the physical disorders which commonly does remain undiagnosed for three or more years Under diagnostic procedures Allan stated: "The blood sedimentation rate and the agglutination test for undulant fever should be determined when there is a suspicion of the hidden infection " Skin tests, opsonocytophagic tests, and cultures apparently were not used in his studies

FEVER

The author has noted fever as high as 106 5° F. in several patients with brucellosis Temperature range from 103 to 105° F. for a period of several weeks is not unusual. There is no definite correlation between the height of fever ordinarily encountered and the degree of prostration or severity of the illness itself There were authenticated hospital temperature records showing temperature elevation to 107 2° F on several occasions in one of the author's patients. An apparently unique instance of extreme hyperpyrexia occurred in a student nurse who was seen in consultation in 1946 Temperature reached 110° F (rectal) on two occasions, preceded by a rise to 108° F. several days before The extreme temperature level was accompanied by apnea, cessation of heart action, and loss of consciousness, followed by response to artificial respiration and stimulants on both occasions. Those

temperatures were authenticated by use of three different thermometers, recorded by three individuals, including the resident physician. Malingering was excluded by the fact that the patient was in coma. (See pp 286 and 438.)

Hughes[360] stated: "At death the temperature in the mouth is about 110° F., but may continue to rise so that 112 to 115° F. had been registered in the internal organs shortly after death" Hughes considered the pyrexia of brucellosis to be quite characteristic. He stated: "The chief characteristics of pyrexia of this fever when compared with that of others are: (1) The variability which exists in the amount and duration of the pyrexia of different cases. The duration is quite indefinite, and follows no rule applicable to even a majority of cases. The daily pyrexial curve may vary between a continuously high temperature and an intermittent one in different cases, or even in the same attack (2) The tendency of the daily maximum and minimum temperatures to form waves or undulations of intensity, of varying character and length in different cases, but with a tendency in individual cases to resemble a primary wave, or of generally decreasing in length and severity as the case progresses" Most observers make no attempt to describe a characteristic fever. All agree that it may reach great height Simpson[631] stated that fevers of 106 to 107° F. (41.1–41 7° C) may be noted. Spink and Hall[632] make no comment about height of fever other than to say that it may be marked and may be sustained, as in typhoid fever, or intermittent as in pyogenic infections In the author's experience it has not been noted to be characteristic.

LOW-GRADE FEVER

In the chronic illness it becomes important to decide whether or not to consider persistent or recurrent oral temperature rises of 99 to 100° F. as symptomatic of an infectious or other physical disease. As has been said, chronic brucellosis is usually not attended by marked elevations of temperature Low-grade fevers must therefore be evaluated

In discussing normal temperature range Reimann[633] stated that

the oral temperature of about 60 per cent of normal adults rests between 36.8° C (98.2° F.) and 37.2° C (98.9° F.). The extremes of temperature within the normal range were 31.6° C. (97° F.) and 37.9° C. (100.2° F.), he considered, with many fewer persons manifesting either extreme.

In 1936 Reimann[558] reported on the study of temperature curves of 16 individuals, at intervals over a long period of time. Five had no complaints other than fever and 11 were regarded as neurotic, having a multitude of bizarre complaints for which no cause could be found. He concluded that a certain proportion of normal individuals have temperatures regulated at levels slightly higher than 37° C. (98.6° F.) and that temperature at these levels is often found in neurotics.

Ernstene,[195] in discussion of this paper stated that "special consideration must be given to the possible presence of chronic brucellosis, for the diagnosis of this condition is frequently difficult." He considered that a diagnosis of physiologic fever may be justified, in the absence of symptoms, provided the patient has been under observation for not less than one year.

In a more recent study on habitual hyperthermia, Reimann[560] described an instance of premenstrual fever. He referred to a case reported in 1932[557] under the title of habitual hyperthermia of a woman, aged 23, whose temperature had been above the average normal on frequent occasions for eighteen years. On prolonged study it was found that there was a regular relation to the menstrual period, the temperature being normal or subnormal during the first half of the menstrual cycle, rising to levels higher than normal at the mid period when the follicle matures and persisting at high levels until the day before the menses when it dropped again. Fourteen years later the patient again came under observation. Temperature records twice daily over two menstrual cycles revealed the same course of events, with low temperature (97° F.) from the first day of the menstrual period to the mid-period, an abrupt rise to 99.3° F. and then a fall to subnormal the day before the next period. There were no other signs or symptoms. Whereas no record of periodic fever in this patient during childhood was

obtained, temperatures at fever levels were noted at the age of 5, continuing later in rhythm with the menstrual period, for thirty-two years. He stated: "In certain otherwise normal women whose temperature rises above normal, prolonged and unnecessary search for the cause of 'fever' is often made unless the temporal relation of the fluctuation to the menstrual cycle is recognized. The problem of diagnosis is greater when a neurosis is also present." Premenstrual increase in existing low-grade fever also is likely to occur in the presence of chronic illness.

One hundred cases of long-continued, low-grade fever of unknown origin were studied in detail in the Mayo Clinic between 1919 and 1930 and reported on by Kintner and Rowntree[401] in 1934. They stated that this type of fever is often designated neurogenic or psychogenic, without sufficient basis. They considered that neurotic manifestations were pronounced in at least 25 per cent of the cases. The authors concluded that the evidence relative to the cause of the fever had not been clarified and that there was need for further investigation rather than the too ready acceptance of an unsupportable explanation. *This view is in accordance with that of the author, that the burden of proof that low-grade fever is of psychogenic origin rests upon the physician who so considers it.*

A group of 36 patients with long-continued, low-grade fever were studied by Hamman and Wainwright[287] An accurate diagnosis finally was made in 10, with a presumptive diagnosis in 6 others. Of the 10 accurately diagnosed 3 were found to have had Malta fever, 2 pulmonary tuberculosis, 2 hypernephroma, 1 Hodgkin's disease, 1 ureteral stricture, and 1 tertiary syphilis. Among the 6 questionable diagnoses were 1 of pulmonary tuberculosis, 1 of mesenteric gland tuberculosis, 1 of tuberculous perirectal abscess, 1 of rheumatic fever, 1 of Malta fever, and 1 of multiple myeloma. The impressive percentage of brucellosis cases would probably be duplicated in other series if the multiple tests for this disease were seriously applied and interpreted. The authors stated: "No doubt the correct attitude for the physician—certainly the safe one—is to admit the general possibility of neurogenic

fever and yet never venture to make this diagnosis." They considered hysteria, psychosis, psychoneurosis, and effort syndrome as possible causes of unexplained low-grade fever. They noted the suggestion, frequently made by others, that some persons may have a thermal regulatory mechanism set at a high level so that a normal temperature for that person might be between 99 and 100. They said: "The suggestion is enticing and it would be a great comfort, when harassed by doubt and uncertainty, to seek refuge in that reassuring conviction. Whether or not actually at times this may be the case, we cannot decide, but if it happens at all, it must happen very seldom, as is clearly demonstrated by the routine observation of the temperature of patients on hospital wards. However, the question has little practical significance, no matter how interesting and important otherwise it may be. Even though the physician be convinced that such anomalies do sometimes occur, he is never justified in making this diagnosis under any concrete circumstances."

Noting low-grade fevers frequently among the women students at the University of Oklahoma, Schmidt and Dorsey[804] attempted to correlate them with the concomitant fatigue and brucellosis. One hundred cases of brucellosis were reported on among women of ages from 16 to 52. Elevated temperatures were present in 87 per cent of the cases, the usual readings being from 99.4 to 99.8°F. Fatigue was an almost universal complaint. Arthritis was a major complaint in 12 women from 17 to 52 years old. Fifty-five per cent of the cases gave both positive skin reactions and positive agglutination tests, 18 per cent gave only positive agglutination reactions, 27 per cent gave only positive skin reactions. The activity of the infection in 27 per cent of the 100 cases was therefore uncertain.

It is obvious that low-grade fever should never be the basis for diagnosis of brucellosis unless accompanied by other clinical and acceptable laboratory evidence of *Brucella* infection.

The persistence of low-grade fever after apparently complete recovery from chronic brucellosis following effective therapy is not infrequent and is difficult to explain. It may be due to con-

tinued mild infection, held in check by the immune reaction in the patient.

Fever of varying degree, usually ranging from 99 to 100° F. (orally) but at times as high as 103° F. in one patient was ignored by various physicians who considered it psychogenic or even an evidence of malingering. It was true that this patient, a Navy veteran, exhibited many evidences of an anxiety neurosis but there was also evidence of a salpingitis, apparently of *Brucella* origin, in addition to various other manifestations of brucellosis. Cultures for *Brucella* had been negative on several occasions. After many previous admissions to Veterans Administration hospitals she again was admitted in late August, 1947, with the statement that her fever had ranged from 102 to 103 for the preceding 3 days. During her few days of hospital observation no temperature beyond 99.4° F. (rectal) was recorded. One staff physician was sufficiently impressed by the history to initiate one more cultural attempt. This time and once subsequently blood yielded *Brucella melitensis*.

Since low-grade fever is commonly a symptom of brucellosis and since the clinical material available in many patients is so sparse, it seems important to ascribe to it its proper significance.

Regional Symptomatology

At the risk of repetition in some instances, various symptoms and symptom complexes and localized pathologic states will be discussed from the standpoint of regional symptomatology. It is hoped that in this manner the great mass of material will be made more accessible.

RESPIRATORY TRACT

Cough

Cough, usually productive of a white, frothy sputum, occurs in acute brucellosis and may be severe and stubborn throughout the febrile stage. It may also be a prominent feature of the chronic illness. Beatty[47] reported that cough was an outstanding symp-

tom in 18 of 47 cases observed by him. About one-third of the 175 patients studied by Hardy and his coworkers [295] had cough, some with mucoid or mucopurulent sputum. Haden and Kyger [283] described a dry, hacking cough and substernal discomfort with negative physical and radiographic findings in one patient; persistent cough and hoarseness in a second; cough with foul greenish sputum with coarse râles and nontuberculous infiltration in the base of the right lung in a third, productive cough with infiltration extending outward from the hilus of the right lung in a fourth, slight hacking cough as a prominent symptom in 28 case histories among 227 reviewed.

Bronchitis

Bronchitis is of relatively common occurrence in acute brucellosis, sometimes suggesting early pneumonia because of moist râles, but without radiographic changes, or progression to patches of lobular or lobar consolidation It has been noted by many [47, 49, 56, 422] in the acute or chronic illness. Paretzky [525] described physical findings suggestive of pulmonary tuberculosis in 2 patients with localized crepitant râles, which disappeared with recovery from brucellosis (p 172)

Hemoptysis

Hemoptysis was reported by Beatty in 5 cases of brucellosis. One instance of frank hemoptysis occurred among the author's cases, in a 34-year-old man whose history pointed to recurrent *Brucella* infection of eighteen years duration Bleeding appeared suddenly in the presence of slight cough, low-grade fever, fatigue, and malaise It was severe, recurring over a period of several days Sputum was negative for tubercle bacilli on more than a dozen examinations Repeated chest radiographs showed no evidence of tuberculosis A violently positive intradermal reaction to heat-killed *Brucella* organisms three years previously and a low opsonocytophagic index at the time of the hemoptysis were the only significant laboratory findings Bronchoscopy revealed an area of ulceration in the trachea Recovery followed vaccine therapy. In

another patient blood-streaked sputum was noted during each of several attacks of pneumonitis accompanying recurrent brucellosis. Haden and Kyger[253] reported hemoptysis in 4 cases among 227 case records of brucellosis.

Pleurisy

Pleurisy, of mild or severe degree, with or without effusion, may occur, especially in the acute phase of brucellosis.[47, 56, 253, 269] Isolation of *Brucella* has been reported[294] from pleural fluid by guinea-pig inoculation.

Four cases of serofibrinous pleurisy, directly attributable to pleural infection in acute and chronic brucellosis, were reported by Maldonado-Allende.[437] He pointed to the infrequent reports of this complication in the literature, and the importance of investigating all serofibrinous pleurisies, pure or hemorrhagic, from the standpoint of *Brucella* infection.

Chest pain, possibly ascribable to localized pleurisy but in all instances confined to the anterior aspect of the upper left chest, was the chief complaint in 6 of the author's patients. All described it as a rather severe but not agonizing pain, steady, usually not dependent on breathing or coughing, not radiating or otherwise suggesting coronary artery pain. Electrocardiograms showed no changes. Temperatures ranged from normal to 99.6° F., in 1 case it was 101° F. Chest signs were absent. One patient refused *Brucella* vaccine therapy and reported the occasional recurrence of similar pain of varying severity. The other 5 patients reported relief of pain, along with other usual symptoms of brucellosis, soon after inception of vaccine therapy.

Empyema

Acute empyema with *Brucella abortus* as the primary causative agent was reported by Macdonald.[403] The clinical course of this empyema was similar to that of a streptococcus infection in that the fluid was seropurulent at the first aspiration, becoming purulent very slowly during subsequent aspirations. No organisms were found on smear or ordinary culture until late in the illness,

when a pure culture of *Brucella abortus* was obtained. This cultural procedure was instituted because it was learned that a routine physical examination made three months before the pres-

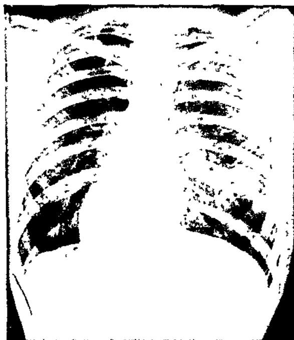


Fig 16 Pneumonic infiltration which cleared slowly under treatment (Courtesy of Dr Oren A Beatty)

ent illness had shown a positive blood-agglutination reaction with *Brucella abortus* Macdonald felt that in acute empyema with a culture repeatedly negative for pyogenic organisms, *Brucella* should be borne in mind as a possible causative agent.

Peribronchial and Hilar Infiltration

Peribronchial and hilar infiltration was described by Beatty [49] in 12 patients with brucellosis Symptoms included cough, expectoration, and chest pain Radiographic findings were characteristic (Fig 16) Bogart [63] reported similar findings

In a 30-year-old patient of the author's, cough, left-sided chest pain, low-grade fever, and unilateral epididymitis began five years following a severe and prolonged acute attack of brucellosis from which he

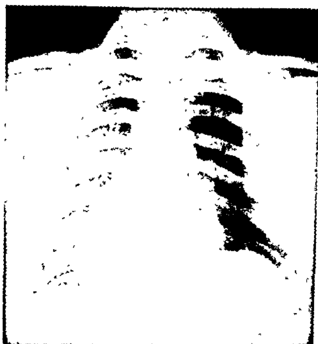


Fig 17 Pneumonic infiltration accompanying subacute relapse of brucellosis with chest pain, low-grade fever and epididymitis five years after severe, prolonged, acute attack Response to *Brucella abortus* vaccine was prompt The chest was entirely clear two months later

had apparently recovered He was ambulatory and still working as a farmhand among infected cattle A radiograph of the chest (Fig 17) showed rather diffuse left-sided pulmonic infiltration, more marked near the hilum Sputum was negative for tubercle bacilli and other pathogenic organisms A month later, following four doses of *Brucella abortus* vaccine, radiographs showed no pathology and all concomitant manifestations had disappeared

Haden and Kyger[354] reported hilar and peribronchial infiltration in 10 among 227 case records reviewed and in 3 cases of their own.

Pneumonia

Bronchopneumonia involving small patches, showing dullness, bronchial breathing, and moist râles was confirmed by radiographic findings[47] Griechener[276] reported bronchopulmonary forms of brucellosis. Lafferty and Phillips[422] described bronchopneumonic processes as well as peribronchial congestion. Robinson,[578] in discussing their findings, observed that these pulmonary changes are common in brucellosis

A 70-year-old woman seen by the author because of an acute illness accompanied by chill, fever of 104° F., and prostration, gave a history of numerous such attacks, of short duration, within the past four years. On one occasion fever and chest symptoms had persisted for three weeks Chest examination showed moist râles at both bases Radiographs (Fig 18) showed pneumonic infiltration of both bases, which slowly cleared The febrile reaction in this instance lasted only twenty-four hours Blood agglutination reaction with *Brucella abortus* was weakly positive, intradermal reaction strongly positive, and opsonocytophagic index low.

One instance of scattered areas of bronchial pneumonia during brucellosis occurred among the author's cases This patient had four attacks within two years, with a chronic cough between attacks Following specific vaccine therapy there was no recurrence during four years of observation.

Hardy and his coworkers[295] reported bronchopneumonia in a patient with brucellosis, at first diagnosed as miliary tuberculosis because of the insidious onset, typical chest physical findings, cough, and mucopurulent sputum Blood-agglutination reaction was positive in a 1 640 dilution and recovery followed.

Radiographic as well as physical signs of diffuse bronchopneumonia closely resembling miliary tuberculosis or carcinomatosis were found in a patient admitted to the author's wards in a naval hospital (Fig 8, p 107)

The patient was a 50-year-old man with fever, malaise, cough, and extremely profuse thin mucopurulent sputum averaging about 24

ounces daily over a period of three weeks. Physical signs were those of bronchopneumonia. The patient was not extremely ill at any time. Sputum remained negative for tubercle bacilli. Blood-agglutination

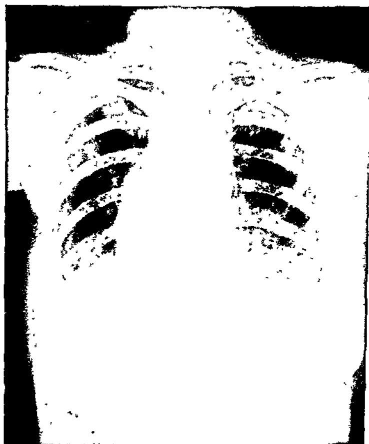


Fig 18 Pneumonic infiltration of bases

reaction with *Brucella abortus* slowly developed to a titer of 1.160. Bronchiectasis was ruled out by further radiographic study after lipiodol instillation as convalescence occurred. Complete recovery ensued.

Nodular granulomas, visualized radiographically, multiple in the right lung, and a single similar area in the left lung of a 42-

year-old man, were reported by Haden and Kyger.[283] He had contracted brucellosis a year before. The areas resembled metastatic malignant disease. They were not present in films taken two and a half and four years later, six years after his first observation he was in good health.

Pulmonary abscess occurred in a fatal case reported by Hardy and his group [295] Both *abortus* and *suis* strains had been isolated from blood. They were uncertain whether one or both varieties of *Brucella* were primarily involved in the production of the abscess or whether it was caused by a secondary invader. Haden and Kyger [283] reported pulmonary abscess as a complication of *Brucella* infection in a 15-year-old girl, who died two months later, the abscess had healed after repeated artificial pneumothorax inductions.

In 1908 Eyre [207] stated: "Pneumonia, generally due to secondary infection with the pneumococcus, also occurs [in Malta fever]. Occasionally a pneumonia primarily due to the *micrococcus* is noted, as in such cases where Fiorentini has recorded the presence of the *micrococcus* in the sputum." Vanni [680] also reported isolation of *Brucella* from sputum.

Johnson [377] reported 3 cases of pneumonia associated with brucellosis In 1 case the onset of brucellosis preceded by two and a half months the pneumonic involvement, which slowly resolved after a prolonged course In 2 other patients symptoms of systemic brucellosis preceded the pneumonic process by about six weeks. In no instance were the patients as ill as would be expected in pneumonia caused by other organisms. Radiographic and physical examination revealed atypical pulmonary lesions which persisted for from thirteen to seventeen weeks.

Unresolved pneumonia or delayed resolution apparently occurs in a larger percentage of pneumonia complicating brucellosis than that of the usual etiology In reviewing the history of 8 cases of unresolved pneumonia reported by the author [279] in 1933, it seems probable that at least 3 of these patients were suffering from pneumonia complicating brucellosis Subsequent study established a definite diagnosis of brucellosis, probably of many years

duration, in 1 patient. In 2 patients treated at later dates, failure of resolution was greatly protracted and apparently was brought about by specific treatment of the *Brucella* infection.

Lobar pneumonia, apparently due to *Brucella* infection, with sputum negative for pneumococci or other likely incitants, occurred in 2 of the author's cases in civilian practice; 2 other cases were encountered in naval service. One was in a Maltese sailor serving in the British Navy. Radiographs showed a fan-shaped area of consolidation radiating from the hilum (Fig. 7, p. 106). The onset and physical and radiographic signs in all cases were as in pneumococcic pneumonia but the course was milder and more protracted than expected. The pneumonic process in 2 patients failed to resolve over a period of several months, resolution followed inception of *Brucella* vaccine therapy.

Simulation of Pulmonary Tuberculosis

Simulation of pulmonary tuberculosis because of low-grade fever, weight loss, night sweats, cough, and vague radiographic changes have led to the admission of many patients to hospitals and sanitaria for the treatment of tuberculosis, in spite of sputums negative for tubercle bacilli. Brucellosis usually is not considered as of possible etiologic importance, or the possibility may be dismissed after a negative blood-agglutination test and without use of other diagnostic measures for *Brucella* infection. In an article entitled "Differential Diagnosis in Pulmonary Tuberculosis," Waring[693] stated that tuberculosis must be differentiated from seventeen enumerated conditions. Brucellosis was not among them.

The following case histories are illustrative.

An 18-year-old girl consulted the author in 1923 because of cough, profuse expectoration, lassitude, low-grade fever, loss of weight, and night sweats of several months duration. After prolonged observation, which included more than 50 negative sputum examinations and repeated radiographic study, a diagnosis of pulmonary tuberculosis was finally made by a consulting chest specialist. She was admitted to a tuberculosis sanatorium. Radiographs never showed definite evidence

of tuberculosis nor was a positive sputum obtained She improved under the rest regimen and was discharged from the sanatorium after four months, to relapse a few months after returning home Subsequent study over several more years failed to reveal evidence of tuberculosis, but fever, cough, sweats, and other symptoms continued to recur. It was not until 1932 that brucellosis was considered as the possible explanation of this long illness The blood-agglutination reaction was negative, the skin test was positive The opsonocytophagic test and cultural facilities were not available Clinical response to *Brucella abortus* vaccine was so marked as to leave little doubt of the diagnosis of brucellosis She remained well under observation for nine years.

A 19-year-old male farm worker was admitted to a sanatorium in August, 1928, with a diagnosis of tuberculosis and discharged in May, 1929 Complaints had been fatigue, low-grade intermittent fever, and progressive weight loss, totaling nearly 40 pounds over a period of two years Radiographs had showed "suspicious changes in both lung fields " Sputum had never showed tubercle bacilli. He improved under the rest regimen and had only vague complaints of recurrent fatigue thereafter until he consulted the author in July, 1937, complaining of pain in the right inguinal region and of "aching of knees and legs." Physical examination and laboratory study were negative, except for a temperature of 99 6° F Skin test was not done and he was not seen again until April, 1941, this time complaining of pain and soreness in the bladder region, painful urination, and recurrent fatigue Examination was negative except for a temperature of 99 8° F Blood-agglutination reaction with *Brucella abortus* was positive in a dilution of 1 10 Phagocytic index was at a low level (0–0–10–15, a numerical index of 10) Skin test with heat-killed *Brucella abortus* organisms reacted strongly, his symptoms were intensified for a few days following which he steadily improved Coincidentally there was a rise in his phagocytic index In August, 1946, he reported that he had had no recurrence of symptoms until the past few weeks Following a single additional dose of 0 1 cc of *Brucella abortus* bacterin there was intensification of symptoms and then clinical recovery, with a commensurate phagocytic response He had returned to the sanatorium in 1944 where the same physician, after reexamination and review of radiographs, had concluded that his illness, recurrent over a period of eighteen years, was brucellosis

Schneider[609] examined the blood of 45 selected cases of apparent pulmonary tuberculosis, finding agglutinins against *Brucella* in 23, in titers ranging from 1:10 to 1:160. Among these 23, sputum was positive for tubercle bacilli in 9 and persistently negative in 14. The possibility that tuberculosis and brucellosis coexisted or that brucellosis simulated tuberculosis in some was discussed.

Two cases of undulant fever with localized pulmonary findings closely simulating tuberculosis were reported by Paretzky.[525] He considered that the râles in such instances are manifestations of an inflammatory condition in the pulmonary parenchyma but not productive of an exudate or of a consolidation sufficiently massive to cast a shadow in the x-ray film, of the nature of "light and abortive bronchopneumonic foci."

CARDIOVASCULAR SYSTEM

Much of the material on affections of the heart and blood vessels is contained in the chapter on pathology.

Pulse, in the acute illness, may be slower than is commensurate with height of fever, resembling the pulse of typhoid fever In the chronic illness, with low-grade or no fever, the pulse exhibits no special characteristics in the average patient but complaints of tachycardia are common, with or without myocardial involvement

Blood pressure usually shows no remarkable changes, except in the presence of complications affecting the cardiovascular system However, in 9 patients observed over a period of years there was moderate to marked hypertension which persisted during active illness and subsided with recovery. The youngest was a boy of 14 and the oldest a woman of 73. The psychologic result attendant upon better health would seem unlikely as an explanation in all instances.

Myocarditis

M[illegible]s frequently has been observed at autopsy. Clinical syr[illegible] myocardial weakness are noted in a large percentage

of patients whose acute illness has been protracted, and in those depleted by years of recurrent infection Helpern [328] furnished the history and a series of electrocardiograms of a 25-year-old man who ran a febrile course with a temperature ranging from 100 to 102° F. from September to November, 1939, and then a chronic course with recovery by September, 1940, except for moderate dyspnea and fatigue Clinical evidence of myocardial damage was tachycardia on mild exertion, moderate dyspnea, and fatigue. There was no cardiac enlargement or murmurs. Other symptoms were sweats, muscle and joint pains, backache, occipital headaches, pyuria, prostatitis, orchitis, and lymphadenopathy. A series of electrocardiograms (Fig. 19) taken at intervals beginning two months after the onset, showed progressive changes, particularly in the P–R interval in lead II and in T waves in lead IV, with reversal toward normal in the last tracing, taken ten months after the first Rubegni [591] called attention to electrocardiographic alterations in the course of Malta fever in 1939

A fatal case of brucellosis in a 57-year-old Michigan farmer was reported; [588] the outstanding findings were: cough, large quantities of tenacious sputum, chills and fever, drenching sweats, generalized arthralgia, dyspnea, edema of the ankles, loss of weight, hepatomegaly, splenomegaly, ascites, leukopenia with slight relative lymphocytosis, positive agglutination reaction in blood and ascitic fluid. Death on the two hundred and eighty-third day of the illness was attributed to cardiac damage (p 94)

Anginal pain, myocardial failure, mediastinal abscess, and ulceration of the aorta with destruction of the anterior cusps were reported [295] in a fatal case of *Brucella suis* infection in a 21-year-old male packinghouse employee This patient had had two attacks of anginal pain on January 14 and 24, 1929 In February evidence of myocardial failure, without constant signs of valvular lesions, appeared and he died on February 21, 1929. Blood culture yielded *Brucella suis* (p 93)

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Myocarditis

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Pericarditis

Pericarditis with effusion has been described by Hughes,[363] and others. Hardy and his coworkers[295] reported pericarditis asso-

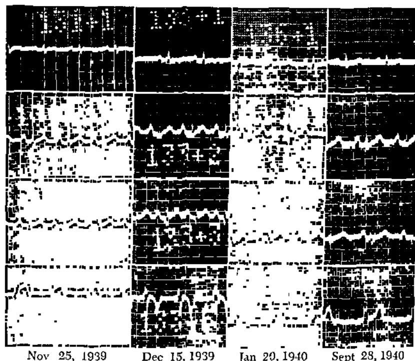


Fig 19 Electrocardiograms of male patient, aged 25, two months after onset of brucellosis, during stage of partial remission Clinical evidence of myocardial damage tachycardia on mild exertion, moderate dyspnea and fatigue No cardiac enlargement or murmurs Temperature range from 100° to 104° F, from September to November, 1939 Sweats, muscle and joint pains, backache, occipital headaches, pyuria, prostatitis, orchitis, and lymphadenopathy Progressive myocardial changes shown Clinical recovery by September, 1940, except for moderate dyspnea and fatigue (Courtesy of Dr Herman Helpern)

Note Rubegni called attention to electrocardiographic alterations in the course of Malta fever in 1939 (Rubegni, R Alterazioni elettrocardiografiche in corso di infezione maltese *Cuore e circolazione*, anno XXIII, Nuova Serie)

ciated with endocarditis in 1 case It is of unusual occurrence in any but the severe acute illnesses

In one chronic illness there were symptoms referable to the pericardium with characteristic radiation and type of pain, low-grade

process in the deep veins at the base of the brain; this patient recovered

The author has observed thrombophlebitis of deep and superficial veins associated with brucellosis in several patients Only through response to specific therapy has the probable etiologic connection with *Brucella* infection been shown.

A 30-year-old woman complained of pain and soreness in one ankle The superficial veins were thickened, reddened, and tender. One week later the redness of the involved veins had spread to healthy contiguous skin; a few days thereafter a similar process began on the other ankle There was a low-grade fever The condition progressed for a month Blood-agglutination and intradermal reactions were positive. Following the first intramuscular injection of *Brucella abortus* vaccine the process flared up for twenty-four hours and resolved completely within four days

A woman of 52 had worn an elastic stocking for ten years as an essential support for a greatly swollen leg, the result of phlebitis She developed an acute illness accompanied by fever, prostration, malaise, and a diffuse skin eruption of legs and buttocks resembling erysipelas in some areas and erythema nodosum in others (page 260) Within a month of her recovery there was subsidence of the swelling of the lower leg and she was able to discard the support From the history of the onset of the phlebitis and its virtual cure following vaccine treatment of brucellosis ten years later it seemed probable that the etiologic agent in the phlebitis had also been *Brucella*

A similar result was attained in a petty officer in the Navy; the left upper extremity had been involved for a year prior to treatment

HEMATOLOGY

Anemia, normocytic or macrocytic, occasionally microcytic, of varying degree may occur at any stage of the disease and may be manifested rapidly, even in patients making good clinical progress Frequent blood studies are essential. There is often no apparent relation between the severity of the illness and the degree of anemia Occasionally it is profound Rarely it closely

ease, in patients with brucellosis were mentioned. Manchester[558] discussed this hypothesis in 1942, noting that coronary arterial disease was present in 26 per cent of a skin-test-positive group in contrast with 3.5 per cent among the negative reactors among 100 patients with chronic complaints. The case histories were suggestive of a causal relationship between brucellosis and coronary arterial disease. In 1 of Manchester's patients there were symptoms and signs of a temporal arteritis and substernal pain precipitated by exertion suggesting coronary arterial disease, electrocardiogram was negative as in the other cases quoted. In the author's case—a 60-year-old man—effort syndrome, with characteristic precordial pain and radiation, recurred periodically for two years. Electrocardiography and all other examinations were negative. He had a low-grade fever with an occasional subacute exacerbation. Blood-agglutination reaction with *Brucella abortus* was positive in a 1 80 dilution, following which an intradermal reaction to heat-killed *Brucella* organisms was violently positive. Subsequently the phagocytic index rose to a high level. From that time on he remained free of symptoms suggestive of coronary arterial disease for the next six years, when death occurred due to prostatic carcinoma.

Thrombophlebitis

Thrombophlebitis was mentioned by Sharp[820] as on record since Cantani's report in 1914 Sprunt and McBryde[848] quoted Wohlwill's report of the death of a woman from pulmonary embolism, found at autopsy to be due to thrombophlebitis of the femoral vein, of *Brucella* origin Bagley, Mueller, and Wells[33] reported death from pulmonary embolism in a 46-year-old laborer suffering from acute brucellosis, due to the *abortus* strain They cited the report[554] of cases of phlebitis complicating brucellosis, in some of which pulmonary embolism occurred; venous localization of *melitensis* septicemia was suggested Also cited was a personal communication from Foshay describing edema and cyanosis about the face and head, attributed to a thrombotic

philic granulation of the neutrophiles were found in all cases. There was no marked increase in monocytes. Both Munger and Calder considered the blood picture suggestive of liver pathology.

Leukopenia with relative lymphocytosis was seen in all of the 17 acute cases of laboratory infections (*Brucella suis* and *melitensis*) reported by Howe and his coworkers.[345] The variable white blood counts and differential counts observed by other workers in acute or chronic brucellosis may be explained on the basis of infection with the *abortus* species in some instances, on strain variations in others, on chronicity of infection in some, and the effect of intercurrent infections in still others.

The leukopenia with relative lymphocytosis so commonly found in brucellosis is not necessarily reversed with clinical recovery. There is no apparently consistent relationship between the lymphocytic–polymorphonuclear leukocyte ratio and clinical or serologic findings.

Diminished coagulability of the blood was noted in some cases by Hughes[359] Although clotting-time observations were not made routinely, the author found diminished coagulability of the blood in 6 patients In 3 patients studied prior to tonsillectomy there was slow clotting time, moderate anemia, and normal platelet counts; treatment of the anemia alone was ineffective in influencing clotting time but there was reversal to normal clotting time following treatment of the apparently underlying brucellosis Calder and his coworkers[104] noted slow clotting time in one-third of the 286 cases, in the presence of normal platelet counts

Eosinophilia of from 5 to 9 per cent, rarely higher, has been noted in about 15 per cent of the author's cases In 1 patient with extreme eosinophilia varying from 45 to 85 per cent with white-cell counts ranging from 7,150 to 13,000, there was a long history of allergy probably preceding the chronic brucellosis in onset and possibly responsible for it. In a second patient with chronic brucellosis (agglutination reaction in a titer of 1 80 and positive stool culture for *Brucella*) eosinophile counts ranged from 35 to 62 per cent with total white counts from 12,800 to 24,000. This patient had had vague chronic symptoms for eight months prior to an

resembles pernicious anemia. Pallor may be marked, usually a dull grey. One patient suffering from severe anemia at the onset of her illness and with each subsequent relapse aptly described her own color as "like the inside of an oyster."

Calder, Steen, and Baker[104] stated that mild anemia of the macrocytic-hyperchromic type was frequently encountered in the study of 286 patients. In only 6 cases of apparently uncomplicated brucellosis were microcytosis and hypochromia observed. Munger,[502] after blood studies in 76 cases of acute brucellosis, all of whom had positive cultures for *Brucella melitensis*, reported a tendency to slight microcytosis with macrocytosis in some.

Leukopenia, usually with relative lymphocytosis,* is a frequent but not constant finding in brucellosis, acute or chronic. Staub[549] reported leukopenia as invariably present in 150 cases of brucellosis occurring in Northwestern United States, a surprisingly uniform finding. Calder, Steen, and Baker[104] reported normal leukocyte counts in one-half, leukopenia in one-third, and leukotysis in one-sixth of 271 bloods studied, figures which roughly correspond to the author's observations Active stimulation of lymphopoietic centers was evidenced in almost all cases. In 76 per cent there were more than 30 per cent of lymphocytes, in 16 6 per cent there were more than 50 per cent Immature lymphocytes were noted in these Plasma cells were found in more than one-third of the cases Monocytes were not increased, Calder noted, in contrast to rather marked increase noted by the author in a small percentage of patients There was a moderate increase in "stab" neutrophiles in many cases.

Among the 76 cases of acute *melitensis* strain infections studied by Munger,[502] leukopenia with relative lymphocytosis and slight monocytosis was noted, with increase in nonfilamented neutrophiles, and in 40 per cent of the cases there were pathologic lymphocytes Liver endothelial cells were found consistently, much larger than normal small lymphocytes, similar to a type of infectious mononucleosis lymphocyte Varying degrees of baso-

* That the lymphocyte plays some role in immunity through production of antibodies was suggested by C H Bunting (Wisconsin M J 24 305, 1925)

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acute febrile exacerbation which occurred in January, 1946 During the acute illness eosinophiles had varied from 2 to 4 per cent. The marked eosinophilia was discovered a month later while he was running a low-grade fever; the chief complaint was fatigue. Eosinophilic leukemia was ruled out by further blood and bone-marrow study. *The eosinophile count returned to normal following recovery under Brucella antigen therapy.* The eosinophilia apparently was due to allergic response to *Brucella* infection

Calder and his coworkers[104] found eosinophilia of 5 per cent or more in approximately one-fifth of the 286 bloods studied. Elson and Ingelfinger[194] reported eosinophile counts of from 29 to 42 per cent in the presence of a leukocyte count of 9,800 to 15,000 in one patient and from 27 to 40 per cent in the presence of white cell counts of 16,600 or higher in another patient, both suffering from chronic brucellosis with pneumonitis.

Blood-sedimentation rates were not determined routinely in the author's earlier cases. In 255 chronic illnesses, sedimentation rates were elevated in 63 (24.7 per cent) and within average normal range in 192 (75 3 per cent), on initial examination. However, fluctuation of sedimentation rates on subsequent determinations during the course of observation and treatment showed rather wide swings. In the patient with chronic pericarditis (p 174), the rate reached 106 mm. (Westergren) In the presence of arthritis and other localized pathology, moderately high rates were the rule. Calder and his coworkers[104] found moderate increase in rate in slightly more than one-third, and very slow rates not uncommonly, with excessively fast rates usually explainable on the basis of complications such as arthritis or effusions. Roberts and Roberts[577] reported normal or slightly increased rates in the presence of arthritis.

Purpura, of varying severity but usually mild, was noted in 7 patients In 1 there was intestinal, subcutaneous, and subconjunctival bleeding in the presence of recurrent splenomegaly, in a second there was massive hemorrhage into both Bartholin's glands,[300] in a third there was menstrual flooding and subcutaneous bleeding, in others subcutaneous extravasations only. Tovar[616]

reported that 7.7 per cent of a group of 650 patients with positive blood cultures presented purpuric complications. Only 0.66 per cent in a group of 300 cases suffering from brucellosis with negative blood cultures had benign purpuric complications. All patients with purpuric complications were infected with the *melitensis* variety, most of them showing prolonged septicemia. Ninety per cent were nonthrombocytopenic purpura.

Blood chemistry has received little attention. Whether or not abnormal findings other than hyperglycemia and alteration of the albumin-globulin ratio are of importance has not been demonstrated. *Hyperglycemia*, with fasting blood-sugar levels from 168 to 280 mgm. were found in 5 of 8 patients presenting glycosuria in the presence of brucellosis. With clinical recovery blood-sugar levels returned to normal. (See pp. 271–272.)

GASTROINTESTINAL TRACT

Hughes[279] felt that the condition of the tongue was a fair index of the patient's condition at the moment and that a fall of temperature to normal would rarely prove permanent unless at the same time the tongue had also become clean. Constipation was the rule in these cases, occurring in about 81 per cent, with alternating constipation and diarrhea in about 3 per cent. Uncontrollable vomiting was a rare complication.

Constipation is a frequent complaint in the acute and chronic illness. It was noted by Hardy and his associates[293] in more than half of the cases, most of whom were acutely ill. It may be severe in the chronic illness.

Diarrhea may occur in the acute or chronic illness, as a major complaint in a small percentage. It may be due to intestinal localization of infection or to psychosomatic factors.

Intestinal brucellosis alone or coexisting with amebiasis was considered by D'Antoni[159] as an important cause of chronic diarrhea. He noted the refractoriness of some cases of amebiasis until the concomitant *Brucella* infection was treated.

Abdominal distention may be a prominent feature of the acute or chronic illness. A 60-year-old woman complained of gradual

enlargement of the abdomen over a period of a year. Her appearance at examination suggested full-term pregnancy or abdominal tumor of other origin. There were no other physical findings. Blood-agglutination reaction with *Brucella abortus* was weakly positive and intradermal reaction strongly positive. Following subsidence of the skin reaction, distension disappeared and had not recurred nine months later. In several other patients response to specific therapy in a less dramatic manner and recurrence of distension with relapses was noted Borborygmus of extreme degree was present in one patient, during the course of a severe chronic brucellosis, responding to specific therapy.

Peptic ulcer as a possible portal of entry for *Brucella* was discussed by Carryer and Prickman.[127] The incidence of peptic ulcer in patients with brucellosis was two and one-half times greater than among those showing no evidence of brucellosis. Although they avoided the conclusion that the ulcerated area was the portal of entry, it was pointed out that proper precautions against infection should be observed all the more assiduously by ulcer patients.

These observations may explain the incidence of peptic ulcer in brucellosis patients reported by the author.[299] Another possible factor may exist in the psychosomatic basis for peptic ulcer.

Right lower quadrant pain and localized tenderness occurring in patients with brucellosis presented problems difficult of evaluation in 13 instances The patients ranged from 9 to 30 years of age Their histories were quite similar. Fever usually was low-grade (99 2 to 100 6° F.); in one instance it was 103° F Pain was seldom diffuse even at the onset, usually being localized in the right lower quadrant and of variable severity. Tenderness was well localized in the appendix region There was moderate muscle spasm in some but actual rigidity of the right rectus in only one Vomiting was absent in all but 2 patients who vomited once Nausea was conspicuously absent in the others White blood cell counts varied from 7,000 to 14,000 In all cases there was laboratory evidence of brucellosis, past or present

Lack of rigidity, relative absence of nausea and vomiting, lack of progressive rise in white blood cell counts, coupled with the

previous history of fatigue, joint and muscle pains, or other syndrome suggesting brucellosis, prompted further observation rather than laparotomy in all but 1 patient. Three patients were known to have had brucellosis previously. The finding of *Brucella* agglutinins or positive skin tests or both suggested brucellosis with possible localization in the right lower quadrant or with referred pain. Further evidence was the clinical response to vaccine therapy, usually accompanied by exacerbation of symptoms and recovery. A few patients relapsed, with recurrence of pain and generalized symptoms, several months to a year later, responding again to therapy Two patients had attacks of typical acute appendicitis, one a year and one two years later, and were operated upon. There was no difficulty in distinguishing these attacks from the previous ones, tenderness was greater, rigidity was present, and the white blood cell count rose commensurately Three other patients were operated upon, contrary to advice, and normal appendices found Two of these continued to have right lower quadrant pain.

A girl of 12 was first seen on the third day of her illness Pain in the right lower quadrant was severe The temperature was 100 6° F, pulse 96, and tenderness was sharply localized in the appendix region. Rectal examination elicited typical appendiceal or cecal tenderness Although the white blood count was within normal range (8,000) there were sufficient other findings, including right rectus rigidity, to indicate prompt exploratory laparotomy The appendix was normal but regional lymph nodes were markedly inflamed The blood-agglutination reaction with *Brucella abortus* was reported after operation as positive in a 1 10 dilution, and a month later in a 1 160 dilution No skin test had been done By then other symptoms referable to chronic brucellosis had developed and fever continued All symptoms subsided following vaccine therapy

Acute or subacute abdominal symptoms, simulating various surgical conditions, have been recognized by several observers Simpson [632] stated that abdominal pain was a prominent complaint in 18 cases of brucellosis, in 5 instances it was most marked

in the right lower quadrant. In 3 out of 4 of these cases normal appendices were found at laparatomy.

Hemorrhage from the bowel occurred in 3 patients. Isolated ulcer of the transverse colon was demonstrated radiographically in 1. The bleeding from the bowel in a 55-year-old woman could not be localized; subcutaneous and subconjunctival bleeding also occurred. In a third patient there was recurrent hemorrhage over a period of fourteen months from a small ulcer just within the anus. In all 3 there was no recurrence following treatment for brucellosis.

Gastric and duodenal hemorrhage in the course of brucellosis was described as relatively frequent by Maldonado-Allende.[456] Melena and hematemesis in a 43-year-old woman was carefully studied to exclude all other causes. Bleeding from ruptured esophageal varices is discussed on page 114.

Other Abdominal Manifestations

Abdominal tenderness, with no significant localization, or simulating definite clinical entities such as cholecystitis, is a fairly common finding At laparotomy no pathology may be found or there may be actual cholecystitis—of *Brucella* or other origin—splenitis, hepatitis, or involvement of retroperitoneal or mesenteric lymph nodes.

Enlargement of the spleen, symptomless or with pain and tenderness, occurs frequently in the acute illness and in a small per- [illegible] In a 59-year-old woman enlarge- [illegible] exacerbation of the long-standing [illegible] intervals the spleen usually was not palpable During the [illegible] reactions to *Brucella* vaccine, enlargement would again be readily discernible, subsiding with the reaction. *In a 20-year-old woman* acute splenitis with severe localized pain and tenderness was a prominent feature of the repeated exacerbations of acute illness, which were attended by extreme hyperpyrexia (p 157). At peri- [illegible] was seen to be moderately enlarged and [illegible] for sple-

nectomy several months later only slight adhesions were found, indicating the temporary nature of the splenitis Histologic and cultural study was negative

Among 17 acutely ill patients who contracted *Brucella suis* or *melitensis* infections during the course of laboratory work the spleen was palpable in only one and then only following pulmonary infarcts.[345]

BILIARY APPARATUS

Cholecystitis

Cholecystitis as a complication of brucellosis has been demonstrated by isolation of *Brucella* from aspirated bile and from the gallbladder wall at operation Clinical recovery may follow successful conservative management of the gallbladder disease or cholecystectomy but the gallbladder may not be the sole focus of *Brucella* infection Illness may persist following operation Chronic cholecystic disease may be closely simulated radiographically, on duodenal drainage, or at laparotomy by brucellosis in the absence of any demonstrable pathology

MacQuiddy and Martin[454] reported cholecystitis in a 41-year-old woman *Brucella melitensis* was demonstrated by guinea-pig inoculation of aspirated bile and the same organism was recovered from the blood stream Hardy and his coworkers[295] reported chronic cholecystitis in brucellosis

Acute infectious cholecystitis in the course of a severe illness due to *Brucella melitensis* infection was reported by Mettier and Kerr[478] The patient was observed for two years following cholecystectomy and remained well (p 115).

Hepatitis and Cirrhosis

Hepatitis, evidenced by enlargement, tenderness, and dysfunction, is now recognized to be at least as frequent as splenomegaly. Mild clinical jaundice, with increased bromsulfalein retention and icterus index, has been noted by the author in several patients. Green[270] reported frank jaundice with clay-colored stools in one patient. Spink and Hall[643] mentioned the well-known affinity of

Brucella organisms for the reticulo-endothelial system, observing that it is not unlikely that cirrhosis of the liver may also occur.

A clinical similarity between chronic infectious (virus) hepatitis and hepatitis occurring in chronic brucellosis was noted by Barker, Capps, and Allen.[40] Capps[112] quoted Watson as having seen cirrhosis of the liver due, he believed, to a chronic *Brucella* infection. Lowbeer[443] reported cirrhosis of the liver as shown by biopsy in a patient with osteomyelitis of the ilium and infection of the gallbladder and liver. A 55-year-old patient of the author's died of rupture of an esophageal varix five years after an acute attack of brucellosis, during which period his chronic illness had apparently been controlled by *Brucella* vaccine therapy.

Brucella suis infection in a 25-year-old hog butcher with marked enlargement of the liver and ascites which was sterile on culture was reported by Zaus and Espey.[735] Blood culture was positive. The spleen was seen to be greatly enlarged on peritoneoscopy. There was marked general improvement following treatment with sulfanilamide but the organism was still recoverable from the blood two months after the onset. Puig[547] described ascites as a less frequent and more serious manifestation.

Hepatitis with jaundice, accompanied by high fever and closely resembling hepatocellular jaundice of other origin, was reported by Chaikin and Schwimmer[149] There was complete recovery, with reversal of the abnormal liver function tests along with recession of the enlarged liver They pointed out that in cases in which recovery occurred within a brief period, the alterations are reversible, but that in chronic cases the marked enlargement of the liver is evidence of hepatic damage which may lead to cirrhosis.

Further discussion of liver damage appears in the chapter on pathology.

URINARY TRACT

Brucella infection is rarely mentioned in discussion of diseases of the urinary tract Braasch[79] stated "If there is any evidence in medical science to which urologists have contributed in recent years, it is an increase in the knowledge concerning the bacteria involved in infection of the urinary tract. . . . In order to treat

urinary infection intelligently, the working knowledge of its bacteriology is essential. . ." The bacteria most commonly found in infected urine were said to be. colon bacillus (including *Aerobacter aerogenes, Pseudomonas aeruginosa*); Gram-negative organisms including members of the genus *Proteus, Pseudomonas,* and *Salmonella;* Gram-positive cocci, staphylococci, streptococci (especially *streptococcus fecalis*), and tubercle bacillus. *Brucella* was not mentioned

Pyuria occurred in about 2 per cent of the author's patients with brucellosis but cultural proof of *Brucella* as the etiologic agent was rarely attempted because of inadequate facilities. In 2 patients Gram-negative organisms having some of the characteristics of *Brucella* but not positively identifiable were found. Recurrent attacks of pyuria in patients with brucellosis, abruptly ceasing following inception of specific treatment, and inability to isolate other pathogens served as the basis for assuming a common etiology.

A 32-year-old woman came under observation in 1925, complaining of recurrent attacks of malaise, low-grade fever, and urinary frequency and burning, of several months duration The right kidney apparently was enlarged and was tender on palpation Oral temperature was usually about 99 6° F Urine on repeated examinations showed many pus cells and from few to many red cells, without other abnormal elements. Renal tuberculosis was strongly suspected. Cystoscopy and study of urine for tubercle bacilli, including guinea-pig inoculation, was noninformative on several occasions No pathogenic organism was recovered Eight years later brucellosis was first considered Blood-agglutination and intradermal reactions were positive Treatment with *Brucella abortus* vaccine was begun There were no symptoms or signs referable to the urinary tract in the following ten years although there were minor relapses with fatigue and low-grade fever, necessitating short courses of vaccine therapy

Hardy, Jordan, and Borts [294] stated that cases with initial symptoms of cystitis and renal tuberculosis have been diagnosed as brucellosis through isolation of the organism from the urine and by blood-agglutination reaction

Pyelitis apparently due to *Brucella* infection was seen in 8 children of varying ages and in 22 adults. The apparent effect of vaccine therapy in terminating attacks and preventing recurrence seemed significant.

Cystitis occurred with relative frequency, alone or with upper-urinary-tract infection, in patients with chronic brucellosis. Many patients gave histories of repeated attacks accompanying other evidences of recurrent brucellosis which ceased after initiation of antigenic treatment.

The presence of *Brucella* in the urine has been noted repeatedly since the early reports by the Mediterranean Fever Commission in 1905 to 1907.[564-569] About 10 per cent of *Brucella melitensis* infections were accompanied by excretion of the organism in the urine. Little was said about actual urinary tract infection. Hardy and his coworkers[295] mentioned that a few patients in their series were first treated as cystitis or pyelitis Mild, transient symptoms of a localized infection, such as burning, pain on micturition, or frequency, occurred in 11 per cent. They were not successful in isolating the organism from the urine although they noted the presence of numerous pus cells in some patients, indicating either secondary infection or localization of the specific infection in the urinary tract.

Nephritis, attributable to brucellosis, has been noted infrequently Extremely severe acute nephritis, suggesting the acute hemorrhagic nephritis of hemolytic streptococcic origin, occurred in a young man during a relapse of brucellosis which followed a prolonged acute phase Other instances of lesser severity were noted, responding to treatment of the systemic illness

Bucco[94] reported albumin and casts in a 12-year-old boy during an attack of brucellosis. Blood culture was positive for *Brucella abortus* When this strain isolated from the patient was injected into rabbits glomerulonephritis was produced.

Nephritis may complicate brucellosis in childhood:

A 4½-year-old girl had exhibited low-grade fever, lassitude, anorexia, and pallor for a year, during which time weight had remained sta-

tionary. There was repeated appearance of moderate amounts of albumin and a few granular casts, usually disappearing in two to three days. Glycosuria was found on several occasions, without reference to other urinary findings. No explanation for these bizarre findings was evident. Because of a history of consumption of raw milk from herds known to be infected, brucellosis ultimately was suspected. Blood-agglutination reaction was negative. An intradermal test with heat-killed *Brucella abortus* vaccine was negative on the fourth day but showed a delayed positive reaction on the seventh. In the absence of other plausible explanation, a therapeutic trial of *Brucella* vaccine was initiated. Response was complete after six doses. She gained 10 pounds within the subsequent six months and there was no recurrence of symptoms during the next fourteen years.

Nephritis with many erythrocytes and granular casts, edema of the legs, with abnormal blood urea and creatinine levels, was reported by Degowin, Carter, and Borts [167] in a patient with *Brucella suis* infection (p. 117).

Albuminuria without casts has been noted in other patients mildly ill with brucellosis, disappearing with response to treatment with *Brucella* antigens.

Nephritis in pregnancy was encountered in the fifth month of gestation in a woman with a history of chronic brucellosis. There was marked edema of the extremities, large amounts of albumin, and many granular casts in the urine. Blood pressure was within normal range. Blood-agglutination reaction was positive. There was recovery, with disappearance of edema and abnormal urinary elements, following antigenic therapy There was no recurrence of symptoms throughout the last four months of pregnancy or during the next two years.

Hematuria was reported in 1911 by Cantaloube and Thibauld [110] It was seen twice among the author's patients:

The mother of a 4-year-old boy noted blood stains on his pajamas twice within a period of six weeks. Urination was painful, with occasional dribbling of pure blood at the end of urination and incontinence. The child was pale and listless, with a daily rise of temperature to 100° F There was no evidence of calculus or of blood dyscrasia. After

cessation of the bleeding moderate amounts of sugar were found in the urine on several occasions. Blood sugar was within normal range Blood-agglutination reaction was negative, intradermal test strongly positive, and opsonocytophagic index low. *Brucella abortus* vaccine produced moderate systemic reactions and exacerbations of dysuria for about twenty-four hours following each of the first four doses; complete clinical recovery ensued. The phagocytic index had risen to a high level by the time nine doses of vaccine had been given. There was no recurrence during the next six years.

The second patient was a 59-year-old farmer suffering from severe sciatic neuritis (p. 231). On one occasion he had awakened with stains of bright red blood on his night clothes. On voiding there was first apparently pure blood, without other symptoms. Urine findings were normal three days later and there was no recurrence during the fourteen months he was kept under observation following recovery.

Glycosuria was found at various times in the course of observation and treatment of 8 patients with chronic brucellosis, afebrile or with low-grade fever. In some glycosuria alone was found, occasionally of severe degree; in others varying blood-sugar levels were noted, from 135 to 260 mgms. There were no concomitant symptoms of diabetes mellitus, except in one patient in whom the diseases coexisted. In all cases, except in the diabetic patient, blood-sugar levels returned to normal and glycosuria disappeared concomitantly with clinical recovery following vaccine therapy, with no dietary control. In the diabetic patient the amount of insulin was greatly lessened. There was no explanation for the phenomenon beyond the conjecture that the pancreatic function was affected directly or indirectly on the basis of infection or allergic reaction Curtis and Kredel [153] noted persistent glycosuria in a patient suffering from thyrotoxicosis and brucellosis, but did not consider that brucellosis was the basic etiologic factor

MALE GENERATIVE TRACT

Epididymitis and *orchitis*, together or singly, occurred in 4 to 5 per cent of Hughes'[349] cases and in widely varying percentages of cases reported by others.

LoPresti-Seminerio[445] reported 3 cases of involvement of testes and epididymis. Gea Gonzalez[239] quoted an instance of orchiepididymitis in which the testes were removed under the impression that the process was tuberculous. Blood-agglutination reaction was "intensively positive" and blood culture was positive. Dumond and Farjot[145] reported one case of orchiepididymitis in the presence of positive blood culture. Simpson[627] reported recovery of *Brucella abortus* from the draining sinus of an infected epididymis. Wainwright (quoted by Sharp) stated that mild orchitis occurs in 20 per cent of *melitensis* infections and in 4 per cent of *abortus* infections. Among 230 adult male patients observed by the author, one or both conditions occurred in 6 (2.6 per cent), all except 1 in the chronic phase.

Noteworthy was the case of a 30-year-old physician whose subjective complaints were fatigue and moderate tenderness of the epididymis (p. 40). There was marked and quite characteristic pallor, in the absence of an important degree of anemia, and tender swelling of the epididymis. Blood-agglutination reaction was positive in a 1:160 dilution. Other etiology having been ruled out, the process was considered to be of *Brucella* origin. In a second patient, aged 25, there was recurrence with each of three relapses of moderate degree, following a severe, prolonged, acute febrile attack. These patients presumably were infected with the *abortus* strain.

De la Cruz[171] stated his belief that orchitis is a manifestation of *melitensis* infection.

Prostatic infection is rarely reported. Boyd[75] reported a serious, protracted, chronic illness in which *Brucella abortus* was recovered from prostatic fluid.*

* McVay and his associates (*Proc Soc Exper Biol. & Med.* 69 607, 1948) re-

cessation of the bleeding moderate amounts of sugar were found in the urine on several occasions. Blood sugar was within normal range. Blood-agglutination reaction was negative, intradermal test strongly positive, and opsonocytophagic index low. *Brucella abortus* vaccine produced moderate systemic reactions and exacerbations of dysuria for about twenty-four hours following each of the first four doses, complete clinical recovery ensued. The phagocytic index had risen to a high level by the time nine doses of vaccine had been given. There was no recurrence during the next six years.

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of remission may give no information Repeated pelvic examinations may be necessary. Recurrence along with other symptoms of exacerbations of brucellosis is often noted. There is usually a purulent or mucopurulent cervical discharge and a tender mass in one or both quadrants It is often difficult to distinguish between involvement of the tube alone and of the tube and ovary. The tubal infection often serves as a focus of infection, apparently preventing recovery until treatment aimed at its eradication is successful.

The role of *Brucella* infection in pelvic disease is not appreciated. In the course of an attempt to determine the experience of gynecologists with culture of biopsy specimens the following comments were received [657] from one of America's largest teaching centers: "I have never encountered a tubal infection caused by *Brucella*. . . ." Adequate cultural study in a large series of tubal infections remains to be done. Apparently it is rarely carried out even in isolated operative cases.*

In a patient from whose uterine discharge *Brucella* later was isolated (p 118), the right tube had been markedly enlarged and tender and readily palpable on several occasions, a week after one such examination the patient was referred to Dr John A. Sampson who found no evidence of pelvic pathology Ten days after this negative examination there was recurrence of right lower quadrant pain, tenderness and tubal enlargement, low-grade fever, and malaise

Amoss [16] reported an instance of salpingitis in a patient with brucellosis, with positive culture of the blood and other tissues (p 92) Both *Brucella* and tubercle bacilli were isolated.

Ovarian Cyst

Ovarian cysts of *Brucella* origin are usually unrecognized. Their occurrence is likely to be reported only by the surgeon or laboratory worker who is interested in *Brucella* infections. Leavell, Poston, and Amoss [4-7] reported isolation of *Brucella* from ovarian

* See footnote page 191

FEMALE GENERATIVE TRACT

Amenorrhea

Irregularity or suppression of menses occurred in many patients with chronic brucellosis. In none was there sufficient anemia to be significant, or other adequate explanation. Usual menstrual cycles were reestablished following recovery. Hughes[269] noted suppression only in the presence of severe, prolonged, febrile illness. Calder[103] stated that menstrual function was normal in less than 40 per cent of the patients under his observation.

Salpingitis

Salpingitis due to *Brucella* infection was confirmed by isolation of the organism from uterine discharge in one of the author's patients (p 118). Among 192 female patients between the ages of 18 and 45, 24 cases of salpingitis (12.4 per cent), apparently of nonvenereal origin, were reported[308] Three additional cases have been encountered since. Few had the advantage of adequate cultural study for *Brucella* but in all gonococcus infection was excluded, as nearly as possible, by blood-complement-fixation tests and repeated smears and cultures Five patients had exploratory laparotomies but no adequate attempt at cultural study of the specimens for *Brucella* was made. None were acute febrile infections.

Clinically there is nothing definite to distinguish *Brucella* salpingitis from salpingitis of other origin which might coexist in a patient with brucellosis, *except its tendency to complete remission and recurrence*, usually along with other symptoms of brucellosis The patient usually runs a low-grade fever, complains of fatigue and of pain and soreness of slight to severe degree in one or both lower quadrants, and may have other symptoms so marked as to mask the pelvic infection It is usually unilateral and often spontaneously improves so that pelvic examination during the stage

ported isolation of *Brucella abortus* from 2 and of *melitensis* from 1 of 34 hypertrophied prostates cultured, *Brucella melitensis* was recovered from 1 of 43 fibrosed fallopian tubes All 4 patients gave histories suggesting brucellosis in the past, all had negative agglutination and positive skin reactions

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[*] See footnote page 191

cysts, as did Kristensen.[416] A tubo-ovarian abscess, developing as a late complication of brucellosis, yielded *Brucella* in one reported instance.[387]

Endocervicitis

Endocervicitis and/or polyposis may accompany the tubal infection, perhaps as direct extension of infection through the endometrium. In one patient there was a single cervical polyp and in another multiple small polyps lined the lower cervical canal. In the latter case there was also unilateral salpingitis. Neither the salpingitis nor the polyposis recurred during twelve years of intermittent observation following electorcoagulation of the cervical canal, pelvic ultrashort-wave diathermy, and vaccine therapy; systemic manifestations of illness disappeared concomitantly.

Abortion

Abortion as the result of *Brucella* infection of the uterus, membranes, or fetus is generally considered to be rare. Gasparri[288] quoted Thierry as having suspected the relationship for some time before 1906 De Forest[166] quoted Larson as stating in 1911 that the blood-complement reaction for brucellosis was positive in a greater number of aborting women than was the Wassermann reaction. Observations made by himself and his colleagues on 11 aborting women convinced him that abortion in the human may be on the same clinical and pathologic basis as in cattle He attempted to prove the relationship bacteriologically but without success. He stated

> It is to be hoped, at any rate, that in the large number of abortions at various periods of pregnancy which occur in women, there are certain cases in which traumata and syphilis can both be excluded and which by their clinical history, character of vaginal discharge and pathologic changes in both fetus and placenta will be sufficiently characteristic to warrant additional clinical reports which will substantiate the theory which the writer has advanced and which he believes to be true. The placentae and the organs of still-born children in such cases should be studied by means of culture and by animal inocula-

tion. Then, sooner or later, some laboratory clinician will appear who will supply the missing link which is now lacking to make the chain of evidence complete.

This prophecy has been fulfilled but the possibility of *Brucella* infection as an etiologic agent still is largely ignored. Whereas causes for abortion, other than trauma, syphilis, and *Brucella* infection, are now known, there is evidence that those instances that are due to *Brucella* infection are unrecognized because of lack of clinical, cultural, and histologic study.

Simpson and Frazier [635] reported 5 patients who had repeatedly aborted among 63 cases of brucellosis studied. They presented no evidence of syphilis and gave serologic evidence of brucellosis, agglutination titers ranged from 1:80 to 1:320. Four of the 5 women gave histories of a febrile illness, the nature of which was not determined, at intervals from three to six years previously. All had consumed raw milk. De Forest has called attention to the fact that in many patients at least two abortions occurred, in his own patient abortion occurred in three successive pregnancies.

Kristensen and Holm [417] reported the isolation of *Brucella abortus* from the placenta of a fetus aborted in the seventh month, in Denmark. Frei [244] isolated *Brucella* organisms from the vaginal discharge of a woman who had aborted ten days previously. Carpenter and Boak [116] reported recovery of *Brucella abortus* from the tissues of a human fetus that was aborted at the end of the fourth month. Schwartz [614] reported a human case of Bang's disease with abortion

Witenstein [718] recorded one case of abortion due to *Brucella* infection Menzani and De Zanche [476] reported the cases of 2 women who aborted following infection with *Brucella abortus*. The organism was isolated in one case and the infection "strongly suspected" in the other

The author [299] described a case of repeated spontaneous abortion with recovery of the organism from uterine discharge:

The patient was a woman of 29 who never had been acutely ill. She lived on a farm and drank raw milk from a herd known to be infected.

cysts, as did Kristensen.[416] A tubo-ovarian abscess, developing as a late complication of brucellosis, yielded *Brucella* in one reported instance.[387]

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brucellosis are found in the foreign literature and that most of the few reports which have appeared in the American literature were prior to 1935 No concerted attempt has been made to study this aspect of *Brucella* infection Routine culture of maternal blood, placenta, amniotic fluid, fetal blood and tissues, and lochia, if carried out with proper technic, undoubtedly would yield confirmatory information in a larger number of cases.

Simulation of Pregnancy

Uterine changes and amenorrhea simulating pregnancy occurred in 4 cases of chronic brucellosis. In each there was a history of possible pregnancy and of amenorrhea of two to three months duration. Enlargement of the uterus and softening of the cervix were roughly commensurate with pregnancy of that duration. There was no nausea or breast changes. Pseudocyesis was not closely simulated. In 2 patients, present illness, urinary findings, and history of severe illness during previous pregnancies seemed to justify therapeutic abortion, without awaiting reports of Friedman tests, so certain seemed the diagnosis. Curettage was done but in neither case did pregnancy exist The pregnancy tests were reported as negative several days following the curettage. The blood-agglutination and skin tests were positive. Menses were reestablished and uterine enlargement subsided only after vaccine therapy was instituted The third case was similar except that therapeutic abortion was not indicated, all signs suggesting pregnancy disappeared soon after institution of vaccine therapy. In the fourth instance tubal pregnancy was simulated.

Pregnancy and Sterility

The effect of pregnancy on the patient with chronic brucellosis is unpredictable In several patients mildly ill with chronic infection, each of several pregnancies was accompanied by intensification of symptoms Those in whom desensitization to *Brucella* and a good degree of resistance to infection were maintained had few if any symptoms referable to brucellosis Many felt well throughout pregnancy.

At the time of the first abortion she was not seen by the author. The second occurred at the sixth month, the dead fetus was macerated and the placenta showed macroscopic areas of calcification (p 120) Laboratory study of the placenta was inadequate, no attempt being made at cultural examination, through error on the part of laboratory personnel. The third abortion, which also occurred at the sixth month, resulted in a living child who died in a few hours. The placenta was necrotic with numerous areas filled with decomposed blood; it was destroyed before culture could be attempted. Profuse uterine bleeding, lasting six weeks following each of the first two abortions, was terminated by curettement in both instances. A copious, malodorous, purulent vaginal discharge, accompanied by right lower quadrant pain and a palpable tender mass in the region of the right tube followed the third abortion. She complained of malaise, fatigue, and left upper chest pain which had been recurrent since before the first abortion. Fever was low-grade (never above 99.6° F., orally). Blood-agglutination reaction with *Brucella abortus* was positive in a 1:160 dilution. Uterine discharge showed an organism of the *abortus-melitensis* group on autopsy of inoculated guinea pigs Treatment of the tubal infection with diathermy and parenteral use of *Brucella abortus* vaccine was followed by apparent cure, with no recurrence of symptoms referable to brucellosis for thirteen years. The patient was sterile after the third abortion (pp 118, 193).

Abortion of twin embryos between the fourth and fifth months in a patient acutely ill with brucellosis was reported by Borts and his coworkers.[74] She had had one healthy child. There was no other discernible cause for the abortion

In citing the author's case of repeated abortions followed by isolation of *Brucella* from lochia after the third abortion, McGinty and Gambrell [471] remarked. "Speculation as to whether brucellosis causes abortion in women should be changed to how frequently it causes abortion." Spink and Hall [618] in 1945 stated that they had not observed a single proven case

Gray [289] reported *Brucella* agglutinins in 15 of 62 women who had had one or more abortions

It is noteworthy that the bulk of the reports on abortion in

Usually the complaint is only of pain and lameness. The recurrence of symptoms in patients with brucellosis with each of several relapses, the intensification of symptoms during reaction to *Brucella* antigen, and the usual improvement following specific therapy furnish clinical evidence of the relationship to *Brucella* infection.

Degenerative myositis involving the supra- and infraspinatus muscles to a marked degree and the deltoids to a lesser degree was reported in a 25-year-old farmer by O'Donoghue and Scott.[819] The degenerative process complicated a spondylitis also attributable to brucellosis. Biopsy of the right infraspinatus muscles showed marked degeneration of the muscle fibers with interstitial round-cell inflammation. Cultures of the muscle were sterile. Blood-agglutination reaction was positive in a 1:320 dilution.

Myotendonitis, due to or associated with brucellosis, affecting almost all parts of the anatomy in the various cases was reported by Chuinard[199] in a group of 16 patients The connection with brucellosis was not proved by culture but was based on blood-agglutination reaction, skin tests, the phagocytic index determinations, and response to *Brucella* vaccine. He speculated as to the likelihood that *Brucella* organisms might attack the tendonous insertion of muscles, producing necrosis and lysis with occasional healing by calcification, and that other cases of subacromial bursitis or tendonitis might be due to *Brucella* infection

Bursitis

Bursitis due to *Brucella melitensis* was described by Kennedy.[595] "Symptoms of subacute rheumatism" involving various joints preceded involvement of the subdeltoid bursa The deltoid muscle became much wasted, with fluctuation of the anterior and posterior borders, rendering the arm practically useless Blood-agglutination reaction was negative but *Brucella melitensis* was recovered from the aspirated fluid

Three instances of *popliteal bursitis*, 2 of *subdeltoid bursitis* and *periarthritis*, and 1 of *prepatellar bursitis* in patients with brucellosis, apparently attributable to it, were encountered among

Sterility in women was ascribed to *Brucella* infection by Hagebusch and Frei.[245] In an unstated number of adult females, 5 presented sterility as one of their complaints. After the administration of *Brucella* antigen these women became pregnant. Sterility for several years prior to treatment of chronic brucellosis, followed by pregnancy soon after conclusion of treatment, was noted by the author in 4 patients.

Tubal pregnancy occurring in patients with chronic brucellosis warrants speculation as to the role played by low-grade tubal infection due to *Brucella*

ORTHOPEDIC MANIFESTATIONS

Myositis

Myositis is a common accompaniment of acute or chronic brucellosis Distribution may be bizarre.

A 22-year-old man complained of swelling and pain of pectoral muscles. There was uniform swelling and rigidity, with little tenderness, which appeared and disappeared concomitantly with other symptoms (lassitude, low-grade fever, and weakness) over a period of several months There was temporary aggravation of the localized symptoms accompanying reaction to skin test and therapeutic doses of vaccine, with subsequent resolution of the process.

A 40-year-old farmer complained chiefly of failure of convalescence following an attack of "grippe or influenza" in the spring of 1939, and of severe precordial pain, radiating to the left shoulder and arm a year later There was no physical or electrocardiographic evidence of coronary arterial disease The chest pain ceased soon after institution of *Brucella* vaccine therapy Following one poorly gauged dose of vaccine which produced an undesirable reaction there was not only recurrence of precordial pain and substernal oppression but there occurred marked swelling of the left pectoral muscles, with palpable, swollen, tender lymph nodes at the axillary border This process persisted for four days and subsided gradually following smaller, reactionless doses of *Brucella abortus* vaccine Subsequent progress indicated the likelihood that myositis of intercostal and pectoral muscles had accounted for the left-sided chest pain

Arthralgia and Arthritis

Arthralgia, frequently described as stiffness, was noted in about one-third of the cases reported by Simpson [637] and by Hardy and his coworkers.[295] It was usually mild, sometimes almost indistinguishable from the general aching. Several of the large joints usually were involved Persistence for more than two months after convalescence was noted in only 3 patients although 14 reported mild or moderately severe joint pains during convalescence, involving knees, shoulders, ankles, hips, and wrists, in that order of frequency. In half the cases only one joint was affected, with swelling or redness in none

Arthralgia is discussed by most observers as a common accompaniment of brucellosis. There is great diversity of opinion as to the occurrence of true arthritis Often no satisfactory distinction between arthralgia and arthritis is made. No survey of large groups of patients suffering from the various types of arthritis, using adequate diagnostic criteria and unprejudiced evaluation of clinical and laboratory data and therapeutic response has been carried out. The peculiar manifestations of brucellosis and the difficulty in interpretation of clinical and laboratory findings have been handicaps to clarification of the problem Response to specific therapy must be used as an important criterion of the etiologic relationship between *Brucella* infection and arthritis in view of the impossibility of obtaining definitive proof from cultural studies.

Use of the blood-agglutination reaction alone as a screening method results in detection of only a small fraction of cases of actual *Brucella* infection, since the agglutination reaction is negative in so large a percentage of chronic illnesses. Use of the intradermal reaction alone results in ascribing many illnesses to brucellosis when, in fact, the patient may have recovered from brucellosis and have maintained skin sensitivity following recovery. Other cases of actual brucellosis, with negative skin tests, will be overlooked Use of culture alone is an inadequate criterion since

the author's patients. Of the 3 cases of popliteal bursitis, aspiration and compression failed to prevent recurrence; *Brucella* vaccine therapy was followed by recovery in 2; the third remained



Fig 20 Periarthritis of shoulder

unimproved. The one instance of prepatellar bursitis developed after a fall in a patient with chronic brucellosis. Repeated aspirations and compression failed to bring about cure; a single dose of *Brucella abortus* vaccine was followed by resolution of the process Cultural studies, using inadequate methods, were negative

The 2 cases of *subdeltoid bursitis and periarthritis of the shoulder* were so nearly identical radiographically as to be indistinguishable from each other (Fig. 20) Relationship to brucellosis had not been suspected until prolonged physical therapy had failed to bring about more than moderate improvement. There was characteristic pain, localized tenderness, and limitation of motion in both Moderate exacerbation and then recovery followed the initial doses of *Brucella abortus* vaccine.

Arthralgia and Arthritis

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Brucella is so difficult to recover, especially in the chronic illness and when caused by the *abortus* strain. Use of the entire battery of tests, and therapeutic trial of specific methods, must be employed.

With sufficiently careful study and long periods of observation reasonably accurate conclusions can be drawn. Control studies are often of doubtful significance since a large percentage of apparently well persons have been infected at some time and therefore may give some laboratory evidence of infection, past or present.

Hardy and his coworkers [295] stated that detectable hydrarthrosis or swelling of the joints was unusual in their cases, occurring in less than 2 per cent. Goldfain's [263] report gave the impression of a very high incidence of arthritis of *Brucella* origin. Fifty-one per cent of 157 patients tested showed a strongly positive agglutination test, or both a positive skin test and a "positive" opsonic index. Thirty-eight cases were treated. Of these, 23 cases were followed. Improvement from moderate to marked degree or apparent cure occurred in a total of approximately 90 per cent of the 23 cases adequately treated with *Brucella* bacterine. (Seven of the 23 cases were symptom-free at the end of treatment and three months later, 14 had moderate to marked improvement and 2 cases were not improved) No clear distinction was made between neuralgia, myositis, "rheumatism," "rheumatoid syndrome," "rheumatic disease," arthralgia, and arthritis.

In summarizing the findings of others of the incidence of arthralgia and true joint inflammation caused by the various strains of *Brucella*, Green and Freyberg [272] stated. "Arthralgia is more common in cases caused by the bovine strain, and joint inflammation, although less frequent than arthralgia, is usually due to the porcine or *melitensis* strain." After a study of 50 patients, 25 of whom had atrophic (rheumatoid) arthritis and the others with symptoms and manifestations not characteristic of any of the common arthritic diseases, periarthritis, and the like, they concluded that arthralgia and other rheumatic symptoms are common in brucellosis and that *temporary*, nonpurulent joint inflam-

mation may occur. They thought that brucellosis is seldom, if ever, a cause of chronic nonpurulent joint inflammation. They contrasted the high incidence of *Brucella* arthritis reported by Goldfain in Oklahoma with the very low incidence they saw in Michigan. They employed all of the multiple tests for brucellosis but their interpretation of the laboratory findings differed in important respects from the author's concepts. Response to therapeutic test doses of *Brucella* vaccine, which has been found to be a valuable criterion, was not employed.

Apparently any type of joint involvement may be due to brucellosis. Consequently, having made a diagnosis of arthritis and finding evidence of probably active brucellosis, it is not certain whether the arthritis is purely coincidental with or attributable to *Brucella* infection (or *Brucella* allergy). Classification as *Brucella* arthritis largely depends upon response to specific vaccine therapy, as evidenced by subjective and objective improvement, favorable radiographic change, and return of elevated sedimentation rates to normal. Typical atrophic and hypertrophic arthritis and mixed types are encountered in which response to specific treatment leaves little doubt as to the etiologic factor.

The actual percentage of arthritis due to brucellosis probably lies somewhere between the very low incidence estimated by Green and Freyberg and the high incidence suggested by a casual reading of the report of Goldfain.

Hardy, Jordan, and Borts [294] stated that "relatively acute as well as chronic septic processes" and also nonsuppurative forms of arthritis were found in Iowa, without further comment on classification. Hardy [290] later stated that arthralgia occurred in 36 per cent of the cases in Iowa and was a prominent complaint in 7 per cent, involving multiple joints. Only occasionally were the joints swollen, red, and very painful; usually there was no detectable physical abnormality. He pointed out that about one-third of the Iowa infections were of *suis* origin, a strain producing joint symptoms less commonly than does the *melitensis* strain but more often than the milder *abortus* infection.

Simpson [628] stated that joint symptoms were an outstanding

feature of the disease in about 10 per cent of the cases encountered in Ohio and that this may lead to its confusion with acute rheumatic fever. He described [629] transient migrating polyarthritis, particularly of the larger joints, leading to confusion with acute rheumatic fever. In describing acute brucellosis, he stated [630] that permanent impairment of the joints usually does not occur. In discussing chronic brucellosis he stated that hydrarthrosis and arthritis may be associated with the acute form of the disease but much more commonly appear several months, or even years, after the often indefinite onset of the chronic type.

This point has been largely obscured in the literature by the failure to make a clear distinction between the acute and chronic phase of brucellosis and therefore between the acute and chronic manifestations of the infection. When convalescence from the acute illness begins the observation of the physician usually terminates; sequelae may not be discovered or associated with the preceding acute illness. The chronic illness is relatively seldom recognized, and therefore its joint and other manifestations may not be evaluated. *When the same patients are seen over a period of many years it becomes evident that the evanescent hydrarthrosis, synovitis, or arthralgia of the acute phase may be followed, perhaps months to years later, by true joint changes reproducing those seen in various types of arthritis of other origin*

In a series of 427 patients [309] with brucellosis treated prior to October, 1944, about equally divided between rural and urban dwellers, there were 74 cases (17.3 per cent) with atrophic or hypertrophic arthritis. Fleeting joint pain and swelling were considered as arthralgia rather than arthritis. Evaluation as to *Brucella* etiology or mere coincidence with brucellosis was made on the basis of clinical and radiographic study, results of the blood-agglutination reaction, intradermal reaction, opsonocytophagic test, and response to specific vaccine therapy Cultural study of synovial fluid or blood was not undertaken routinely because of inadequate facilities All cases were followed for periods of from one to twelve years.

The usual distribution of arthritis associated with brucellosis

was in the larger joints, although no joint has been without involvement in some patients.

A predilection of a subacute or chronic arthritic process for the metacarpophalangeal joint of the thumb was noted in 11 patients, in the presence of clinical and serologic evidence of brucellosis, usually with no other joint involvement In 5 of these patients the discomfort was from mild to moderate, sometimes described as a lameness such as experienced following a sprain. Radiographs showed no bone or joint changes except for synovial swelling All responded in a characteristic fashion, with exacerbations and then recovery following *Brucella* vaccine therapy. In 2 other patients other small joints were involved in a subacute, painful, crippling process. Multiple small-joint involvement may occur.

Arthritis of the sacroiliac synchondrosis, alone or in association with sciatic neuritis, is not infrequently seen in patients with chronic brucellosis Hughes [369] reported effusion with consequent intense pain Those observed by the author have been of milder nature, without effusion and often with no history of trauma Patients who had been bedridden for weeks, with little or no relief from support, physical therapy, or other measures, responded significantly to *Brucella* vaccine therapy

Rheumatoid arthritis in rare instances apparently may be caused or simulated by brucellosis [305] The following case histories are illustrative

A white man, aged 21, when first seen on September 9, 1941, had been bedridden for a year because of involvement of knees, hips, sacroiliac joints, and of the right shoulder in an arthritic process which had been steadily progressive since 1935 Hip joints were approaching ankylosis Fever had ranged from 99 to 100° F. daily with a high point of 102° F Tachycardia and lassitude had been present throughout Sedimentation rates had ranged from 28 mm. to 55 mm. per hour (Westergren) There had been a loss of 30 pounds in weight. All known methods of treatment had been given adequate trial with little or only temporary improvement Definite radiographic changes had first been noted in March, 1936, when both sacroiliac joints had been found to be about equally involved In November, 1939, radiographs



Fig 21 A Marie-Strumpell type of rheumatoid arthritis, March 20, 1941 (three years after onset) Obliteration of sacroiliac articulations, atrophic process in hip joints B Further progression, August 13, 1941 C Beginning reversal of process in hip joints, December 6, 1941, three months following initiation of *Brucella* vaccine therapy D Marked restoration of articular surface of hip joints, July 2, 1942

C



D

had shown "considerable condensing osteitis about both sacroiliac joints, with generalized decalcification of pelvis and spine, and little involvement of the posterior intervertebral joints, characteristic of Marie-Strumpell arthritis." Subsequent serial radiographs had shown progressive involvement of the hip joints and finally obliteration of sacroiliac joints.

There was a history of consumption of raw milk from infected cows between 1926 and 1940. Blood-agglutination test was negative, intradermal test was weakly positive. The opsonocytophagic test indicated slight resistance to *Brucella* infection, with marked phagocytosis in 2 cells, moderate in 3, slight in 9, and none in 11 cells, a Foshay index of 26.

A therapeutic trial of *Brucella abortus* vaccine was begun on September 29, 1941. Within three weeks of the initiation of vaccine treatment, improvement was noted, first in hip joints. On October 20, 1941, the patient was able to sit up on the edge of the bed for an hour. Fever gradually lessened Sedimentation rate did not consistently parallel improvement. On November 15, 1941, seven weeks following the inception of *Brucella* vaccine therapy, the patient was walking with the aid of crutches. The left hip was still fixed in extension. The phagocytic index showed a steady increase (on November 15, 1941, 12–11–2–0—a Foshay index of 83, on December 6, 1941, 16–9–0–0, an index of 91) Vaccine was continued, with no focal or general reaction at any time In December, 1942, fifteen months later, he had sufficiently recovered to take a fulltime job and he has worked steadily since. Treatment was discontinued in March, 1944, and reinstituted in August, 1944, following 2 attacks of iritis, involving both eyes separately, attributed to brucellosis by the attending ophthalmologist.

The first radiographic evidence of reversal of this supposedly irreversible process was noted in films made in December, 1941, three months after the inception of specific therapy Films made in July, 1942, showed almost complete restoration of hip joints (Fig 21 on pages 206 and 207). However, full function was not restored Six years later there had been no recurrence

A 19-year-old girl was seen in consultation with Dr. Andrew M. Campbell Ten years before there had been a rather sudden onset of illness with chill and fever reaching 104° F., accompanied by generalized rash, painful joints, headache, and prostration. The illness sub-

sided after several weeks She remained well for about a month, after which all of her symptoms returned for a period of six weeks. A diagnosis of rheumatic fever was made. Following recovery she began to have increasing difficulty in walking, with pains in both hips and stiffness of the knees. She had several recurrences of fever, rash, and exacerbation of joint involvement During one attack the rash was thought to be scarlet fever. In April, 1939, a diagnosis of Still's disease was made. She was unimproved after physical therapy, Sutter fasciotomy, application of casts, manipulation, and other procedures Sedimentation rate was never over 36 mm. per hour (Westergren), blood counts were essentially normal except for relative lymphocytosis Fever ranged from 97 6 to 101° F for periods of from four to six weeks, with normal intervals of from six to eight weeks.

In March, 1943, she developed severe headaches and recurrence of fever which persisted for six weeks. Dr. Campbell then suspected the inadequacy of diagnosis of Still's disease. She had lived on a farm and had drunk raw milk prior to the onset of her illness Blood-agglutination reaction and culture for *Brucella* were negative. Intradermal test gave an atypical positive reading. Phagocytic index was reported as "negative."

A therapeutic trial of *Brucella* vaccine was begun in December, 1943. Improvement began within a few days following the skin-testing dose of vaccine, was clinically noticeable within two weeks, and continued She was able to walk without assistance within three months Hip joints regained about 60 per cent of normal motion as compared with about 30 per cent of normal range previously Knee joints improved to about 40 per cent of normal range, from 10 per cent Phagocytic indices done serially indicated marked coincidental increase in specific resistance. Temperature lessened during vaccine therapy In July, 1944, there was another febrile episode with temperature to 101° F During four days of sulfadiazine therapy toxic symptoms developed but temperature became normal, the fever recurring twenty-four hours after the drug was stopped *Brucella* vaccine was then resumed Fever subsided within a week and remained within the normal range for two and a half months Radiographic reexamination in June, 1944, *showed no change as compared with previous films* In January, 1948, Dr Campbell reported that improvement had continued and that the patient was ambulatory and working, with no further exacerbations.

Osteoarthritis, indistinguishable from that of other origin except through discovery of coexisting *Brucella* infection and significant response to specific vaccine therapy was seen in 8 patients. Although cure obviously could not be accomplished in the presence of advanced osteoarthritic changes, relief of joint pain and lameness following treatment was one of the criteria of diagnosis in all. In 2 early cases, with minimal changes, there was complete resolution and no recurrence during the periods of seven and ten years of follow-up.

The following case illustrates advanced osteoarthritis, observed over a period of ten years:

A 55-year-old farmer complained of pain, lameness, and limitation of motion of both hips, and of recurrent malaise and fatigue of several years duration when first seen in 1938 Radiographs showed typical productive changes He had bought and sold cattle and had also served as his own veterinarian on many occasions, removing membranes from aborting cattle in his own herd and those of his neighbors. Blood-agglutination reaction with *Brucella* was negative, intradermal reaction strongly positive, and phagocytic index low. Accompanying the reaction to the intradermal test there was marked accentuation of the pain, lameness, and stiffness of the hip joints. Subtolerance doses of *Brucella abortus* vaccine were followed by slow but steady improvement He was able to return to his arduous farm duties within three months Many times during the ensuing nine years he tried to leave off vaccine but it was found that intermittent courses or a minimum of one reactionless dose monthly was essential to keep him ambulatory. The bony deposits were progressive but the inflammatory reaction was favorably influenced by the apparent desensitizing effect of *Brucella* vaccine and maintenance of a high phagocytic index Definite correlation between intensification of symptoms and a notable fall in phagocytic power of the white cells and between improvement and significant rise in the opsonic test was noted on more than a dozen occasions. Only when *Brucella* vaccine was employed in reactionless doses, was there clinical response

Early in 1946, after three months without vaccine treatment, lameness and swelling developed in the left wrist joint and became progressively worse, along with exacerbation of hip-joint symptoms Pha-

gocytic index was at a low level. Following reinstitution of vaccine therapy there was prompt subsidence of wrist-joint involvement and lessening of pain, lameness, and limitation of motion in the hips That at least part of the joint reaction was of an allergic nature was suggested by the fact that contact with infected cattle was frequently followed by exacerbation of joint symptoms within twenty-four hours

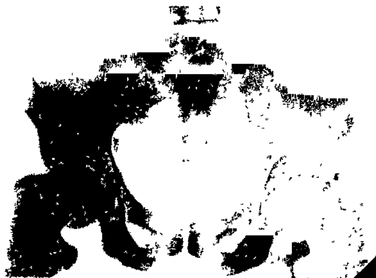
Early osteoarthritis, with reversal of the process, was noted in the following patient:

A 51-year-old man complained of fatigue, malaise, and lameness of the left hip, gradually developing over a period of one year. Radiographs showed a minimal osseous deposit in the left hip joint (Fig 22) Examination was otherwise negative. Blood-agglutination reaction was positive in a low dilution, opsonocytophagic reaction showed moderate resistance to *Brucella* infection, and intradermal reaction was positive. Intermittent *Brucella abortus* vaccine therapy was followed by clinical recovery A year later there was almost complete absorption of the osseous deposit There has been no recurrence in the ensuing seven years

Osteoarthritis of one or both hips, with or without collateral involvement of the vertebral column, was found in 6 other patients associated with chronic brucellosis Degenerative changes in the ilei and femoral heads were noted in several (Fig 23) The process was not considered to be attributable to *Brucella* infection unless there was characteristic improvement under reactionless doses of *Brucella abortus* vaccine.

Mixed types of arthritis were encountered in 2 patients, both involving the knee joint, with degenerative and proliferative changes

An 80-year-old woman complained of progressive lameness, pain, and limitation of motion of the right knee of about seven years duration, latterly necessitating the use of a cane There was moderate swelling and tenderness Radiographs showed destructive and proliferative changes involving the medial aspect of the knee joint, with thinning of the articular surfaces (Fig 24) Blood-agglutination reaction was negative, intradermal reaction positive, and phagocytic



A



B

Fig. 22 A Early hypertrophic changes of left hip, 1939 B Almost complete absorption, with cessation of symptoms, one year later, following *Brucella* vaccine therapy.

index showed slight resistance to *Brucella* infection There was no improvement following two months of diathermy and other physical therapy and the use of a crutch became necessary. Improvement was



Fig 23 A and B Osteoarthritis of hip Hypertrophic spur formation of lumbar vertebrae Degenerative changes in ilium and head of femur

noted within three weeks after inception of *Brucella abortus* vaccine therapy, each dose of which was followed by slight focal and systemic reaction Within three months she was able to walk without the aid of cane or crutch Fatigue, malaise, and low-grade fever lessened The phagocytic index rose slowly There was no recurrence during the remaining four years of her life

A 67-year-old woman complained of stiffness and lameness of the right knee of two months duration, with no systemic or other localized manifestations Radiographs showed osteoarthritic changes in both knees as well as an atrophic process with thinning of the medial articular surface (Fig 25). The opsonocytophagic reaction indicated a mod

erate resistance to *Brucella* infection. Blood-agglutination reaction was negative and intradermal reaction positive. Symptoms referable to the knee joint were completely relieved during the course of six reac-

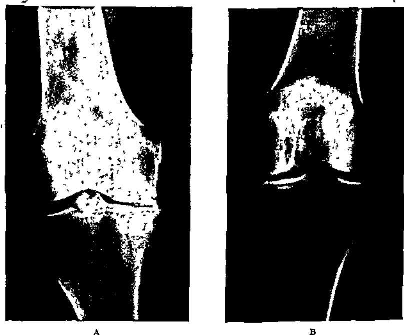


FIG 24 A Degenerative and proliferative changes of right knee in 80-year-old woman B Left knee

tionless doses of *Brucella* vaccine. There was no opportunity for follow-up beyond one year during which she remained free of symptoms.

Effusion (hydrarthrosis) in one or more joints, acute or subacute in nature, was found in about 40 per cent of Hughes'[369] patients in Malta It was usually of sudden onset and short duration, disappearing from one joint and reappearing in others Pain was most intense when vertebral or sacroiliac joints were attacked Failure of response to salicylates was mentioned Suppuration was not encountered.

Hydrarthrosis was encountered in only 1 case among the 375 reported on by Hardy and his coworkers[295] Simpson and Fra-

zier[835] had reported 1 case in which *Brucella abortus* was cultured from the joint fluid. Baker[34] reported *intermittent hydrarthrosis* of both knees, occurring in precise seven-day cycles; *Bru-*



Fig 25 Atrophic and hypertrophic changes in right knee, with thinning of medial articular surfaces

cella abortus was recovered from the synovial fluid from both knees, and from the blood and urine, although the blood-agglutination reaction was negative He observed that arthralgia had long been recognized as part of the symptom complex of brucellosis but that true arthritic changes had not been emphasized. Sharpe[821] also reported hydrarthrosis of the intermittent type. Antonine and Coulon[26] reported simple hydrarthrosis in a 15-year-old patient who developed a painful swelling of one knee

two and a half months following apparent recovery from a prolonged attack of acute brucellosis. The yellowish, slightly opaque synovial fluid agglutinated *Brucella* in a 1:640 dilution and yielded *Brucella melitensis*. Blood-agglutination reaction was positive in the same titer.

Septic arthritis in the hip of a 12-year-old girl was reported by O'Donoghue.[514] Thin pus was evacuated at operation and *Brucella melitensis* recovered Ankylosis resulted.

Suppurative arthritis after operation on a wrist was described by Kulowski.[415] A small amount of seropurulent material was evacuated from the radiocarpal joint. The lateral half of the semilunar carpal bone was roughened, sclerotic, and somewhat loose, and the contact surface of the scaphoid bone was slightly involved. Zdrodowski and Breun [736] reported bone or joint lesions occurring experimentally in 17.5 per cent of guinea pigs inoculated with *Brucella abortus*.

Manson-Bahr [481] reported an acutely ill patient with periarthritis of the carpus who completely recovered after the administration of sulfanilamide, blood culture was positive.

Hardy [290] mentioned spondylitis, arthritis, and osteomyelitis due to *Brucella abortus* infection and quoted one instance in which the small bones of the wrist were involved, the lesion was described as an eroding, suppurating arthritis when occurring in the wrist joint or the spine.

A degenerative process involving all of the carpal bones, suggesting an early suppurative arthritis or osteomyelitis, occurred following a mild injury.

A 60-year-old man complained of pain, tenderness, and swelling of the left wrist joint and carpal region beginning about six days after he had twisted his left wrist when a loghook slipped while rolling a log The condition remained the same, with redness, swelling, and tenderness involving the dorsum of the carpal region, for about six weeks, then improving slightly under thermotherapy. Radiographs showed uniform lack of detail in the carpal bones and the intercarpal joint spaces with apparent fusion and damage to the wrist-joint surfaces (Fig. 26) A year later the condition of the wrist was unchanged

and at that time *Brucella* infection was first considered. Blood-agglutination reaction was positive in a low dilution of the serum and the intradermal test was strongly positive Following institution of *Brucella*



Fig 26 A Degenerative process involving carpal bones of left wrist following trivial injury B Right wrist.

vaccine therapy swelling and tenderness steadily lessened with recovery of more than half of the functional loss.

A "fixation" abscess of bone due to *Brucella* was reported by Edwards,[183] occurring at the site of a bone plate put in place for a fractured femur fifteen years before The patient gave a history of ingestion of raw milk but had exhibited no clinical evidence of brucellosis at any time. Blood-agglutination reaction was positive in a 1 · 1000 dilution against his own organisms, blood culture was negative but pus yielded *Brucella*.

Degenerative changes in the ilium and femur, presumably referable to brucellosis were seen in an aged woman.

An 89-year-old woman with symptoms referable to brucellosis dating back nine years, fell, injuring the region of the left hip A radiograph of the pelvis showed no fracture but extensive degenerative changes in the left ilium and head of the left femur (Fig 27). This patient had

two and a half months following apparent recovery from a prolonged attack of acute brucellosis. The yellowish, slightly opaque synovial fluid agglutinated *Brucella* in a 1:640 dilution and yielded *Brucella melitensis.* Blood-agglutination reaction was positive in the same titer.

Septic arthritis in the hip of a 12-year-old girl was reported by O'Donoghue.[515] Thin pus was evacuated at operation and *Brucella melitensis* recovered. Ankylosis resulted.

Suppurative arthritis after operation on a wrist was described by Kulowski.[419] A small amount of seropurulent material was evacuated from the radiocarpal joint. The lateral half of the semilunar carpal bone was roughened, sclerotic, and somewhat loose, and the contact surface of the scaphoid bone was slightly involved. Zdrodowski and Breun [736] reported bone or joint lesions occurring experimentally in 17.5 per cent of guinea pigs inoculated with *Brucella abortus.*

Manson-Bahr [461] reported an acutely ill patient with periarthritis of the carpus who completely recovered after the administration of sulfanilamide, blood culture was positive

Hardy [290] mentioned spondylitis, arthritis, and osteomyelitis due to *Brucella abortus* infection and quoted one instance in which the small bones of the wrist were involved, the lesion was described as an eroding, suppurating arthritis when occurring in the wrist joint or the spine.

A degenerative process involving all of the carpal bones, suggesting an early suppurative arthritis or osteomyelitis, occurred following a mild injury

A 60-year-old man complained of pain, tenderness, and swelling of the left wrist joint and carpal region beginning about six days after he had twisted his left wrist when a loghook slipped while rolling a log. The condition remained the same, with redness, swelling, and tenderness involving the dorsum of the carpal region, for about six weeks, then improving slightly under thermotherapy Radiographs showed uniform lack of detail in the carpal bones and the intercarpal joint spaces with apparent fusion and damage to the wrist-joint surfaces (Fig. 26) A year later the condition of the wrist was unchanged

and at that time *Brucella* infection was first considered. Blood-agglutination reaction was positive in a low dilution of the serum and the intradermal test was strongly positive. Following institution of *Brucella*



Fig 26 A Degenerative process involving carpal bones of left wrist following trivial injury B Right wrist

vaccine therapy swelling and tenderness steadily lessened with recovery of more than half of the functional loss

A "fixation" abscess of bone due to *Brucella* was reported by Edwards,[188] occurring at the site of a bone plate put in place for a fractured femur fifteen years before The patient gave a history of ingestion of raw milk but had exhibited no clinical evidence of brucellosis at any time. Blood-agglutination reaction was positive in a 1 1000 dilution against his own organisms, blood culture was negative but pus yielded *Brucella.*

Degenerative changes in the ilium and femur, presumably referable to brucellosis were seen in an aged woman·

An 89-year-old woman with symptoms referable to brucellosis dating back nine years, fell, injuring the region of the left hip A radiograph of the pelvis showed no fracture but extensive degenerative changes in the left ilium and head of the left femur (Fig 27) This patient had

two and a half months following apparent recovery from a prolonged attack of acute brucellosis. The yellowish, slightly opaque synovial fluid agglutinated *Brucella* in a 1:640 dilution and yielded *Brucella melitensis*. Blood-agglutination reaction was positive in the same titer.

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had various symptoms referable to brucellosis six years before (p 483). Blood agglutination had been positive in high titer and she had made complete recovery following *Brucella* vaccine The only complaint referable to the hip and pelvis prior to the injury had been of occasional twinges of pain in the left inguinal region over a period of several years.

Osteomyelitis

Osteomyelitis has been described by Hughes[369] and others[429, 446, 630, 636] Kulowski described osteomyelitis of the humerus (Fig. 28) in one patient and of the skull and ribs in another; cultures were positive for *Brucella* No characteristic clinical or pathologic manifestations to distinguish *Brucella* osteomyelitis from that of other etiology have been noted. Recognition depends upon laboratory findings. Although likely to heal after surgical drainage, recurrent, spreading infection may occur in spite of adequate drainage

Recurrent osteomyelitis of the femurs in a girl has been observed by the author over a period of twenty-three years

A 12-year-old girl was first seen in 1924 because of persistent pain in one thigh and calf, accompanied by a moderate degree of malaise and low-grade fever Radiographs showed osteomyelitis involving the lower third of the left femur (Fig 29 *A* and *B*) At operation a low-grade osteomyelitis was found and a Gram-negative coccus or coccobacillus with morphologic, staining, and cultural characteristics of *Brucella* was isolated but not identified as *Brucella* The patient was well until 1929 when a similar process developed in the right femur (Fig 29 *C*) A small medullary abscess was found at operation with similar cultural findings (Fig 29 *D* and *E*) Following the third operation the patient had more or less continuous pain in the thighs for the next five years

She was seen again in 1935 when she was 23 years old, eleven years after the onset of her illness On this occasion her complaint was left-sided pelvic pain and marked tenderness on palpation Temperature was 100° F The tender mass in the region of the left tube suggested



Fig 27. Degenerative changes in left femoral head and ileum in 89-year-old woman complicating severe prolonged chronic brucellosis



Fig 28 Osteomyelitis of head of humerus, showing healed lesions two years after operation at which *Brucella* was isolated (After Kulowski Courtesy of *Surgery, Gynecology and Obstetrics*)



Fig. 29. c. 1929

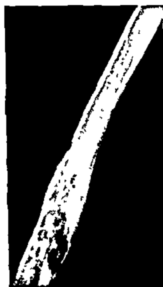






Fig 29 A 1924



Fig 29 B 1924

Fig 29 A-K Osteomyelitis of femurs Series of films taken from 1924 to 1946 Steady progression of disease in spite of surgical drainage in 1924, 1929, and 1930 Arrest of activity following *Brucella* vaccine therapy initiated in 1935 Fracture of the left patella (Fig 29 K) was the result of direct trauma



Fig 29 i 1939



Fig 29 j 1940



Fig 29 k 1946



Fig 29 F 1935



Fig 29 G 1938



Fig 29. H. 1938

therapy. Further radiographs in 1939 and 1940 (Fig 29 *I* and *J*) showed quiescence of the osteomyelitic process. Diabetes insipidus and hyperparathyroidism were ruled out by complete radiographic and blood and urine chemistry studies. Osteitis fibrosa cystica (von Recklinghausen's disease) had been suspected by one consultant because of the widespread involvement of femurs, and its somewhat cystic character. The opinion of Dr. Ross Golden after viewing the radiographs, and that of Dr. Sidney C. Werner from the endocrine standpoint, were in agreement with the original diagnosis of osteomyelitis

Radiographic studies were repeated in 1946 (Fig 29 *K*), twenty-two years after she was first observed There was evidence of still further clinical improvement but she was still dependent upon vaccine therapy, intermittently. It was determined again that low-grade fever, weakness, and pain in thighs recurred only in the presence of depressed phagocytic indices, with marked alleviation or disappearance of symptoms when resistance was restored to satisfactory levels. Thirst had markedly diminished, perhaps because of better insight, or perhaps because improvement in the somatic illness allowed better adjustment to her emotional problems.

Osteomyelitis of both ilia and the coracoid process of one scapula was reported by Smith and by Lowbeer.[636] The patient, a 65-year-old dentist, had had sciatica for five years with afternoon fever for the latter two. He had lost weight and complained of pains in the chest and of cough. An abscess developed in the region of the left hip and in the left axilla, from which *Brucella suis* was cultured Other complications were pyuria, pleural effusion, and cholecystitis Pathologic findings are discussed in detail on pages 129–131. Clinically this illness resembled tuberculosis.

Spondylitis

Spondylitis of *Brucella* origin is of frequent occurrence Kulowski and Vinke [420] reported the first culturally proved case in 1932, although Strachan (quoted by Bishop) [61] had described the lesion in 1911, and Roger (quoted by Gautier) [249] in 1926

The patient of Kulowski and Vinke was a 33-year-old farmer who developed low back pain of insidious onset over a period of about seven months before admission to hospital. Pain was constant, dull,

tubal pregnancy or salpingitis. The uterus was moderately enlarged and the cervix somewhat soft. The process subsided within twenty-four hours and temperature became normal. Blood-agglutination reaction with *Brucella abortus* occurred in a low dilution of the serum. Radiographs (Fig. 29 *F*) showed osteomyelitis involving extensive areas of both femurs; some areas showed signs of healing and in others the condition was apparently advancing.

Brucellosis was then considered as the possible explanation of the long history of recurrent osteomyelitis, the recent pelvic condition, and her inability to regain lost weight. On reviewing the history with Dr. Arthur Elting, who had performed the three operations, he concurred in the opinion that the organism, isolated in 1924 and again in 1929, was *Brucella*.

Response to treatment with *Brucella abortus* vaccine seemed to confirm the provisional diagnosis. Moderate reaction (local, focal, and general) accompanied by exacerbation of pain in both thighs followed closely after each of the earlier intramuscular injections. Improvement became apparent within a month, except for exacerbation of left tubal pain with each menstrual period during the next six months. Ultra-short-wave diathermy through the pelvis was used as an adjunct to vaccine therapy. After treatment was begun in 1935 there was no further extension of the osteomyelitic process. Radiographs taken three years later showed regression of the process (Fig. 29 *G* and *H*). The patient gave birth to a healthy baby that year. Vaccine therapy had been continued at weekly intervals Whenever it was left off for more than a few weeks there was recurrence of pain in thighs, and malaise and low-grade fever. There was definite correlation between her clinical condition and the maintenance of a good degree of resistance as measured by the phagocytic index

Prior to pregnancy she had ulceration of gums and necrosis of the alveolar processes, resulting in the loss of 15 teeth. During pregnancy she developed an extreme degree of polydipsia and polyuria. Urinary output reached 8 to 9 liters in twenty-four hours She voided from six to eight times in the night and at intervals of from 1 to 3 hours during the day. It was considered that this excessive thirst was of psychic origin, with the usual implications There was no doubt, from frequent clinical observation over a long period of time, that there was definite correlation between her state of physical health and the degree of resistance to *Brucella* infection which was maintained by vaccine

therapy. Further radiographs in 1939 and 1940 (Fig 29 *I* and *J*) showed quiescence of the osteomyelitic process Diabetes insipidus and hyperparathyroidism were ruled out by complete radiographic and blood and urine chemistry studies Osteitis fibrosa cystica (von Recklinghausen's disease) had been suspected by one consultant because of the widespread involvement of femurs, and its somewhat cystic character The opinion of Dr. Ross Golden after viewing the radiographs, and that of Dr. Sidney C Werner from the endocrine standpoint, were in agreement with the original diagnosis of osteomyelitis

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The patient of Kulowski and Vinke was a 33-year-old farmer who developed low back pain of insidious onset over a period of about seven months before admission to hospital. Pain was constant, dull,

and aching, not related to activity but relieved by recumbency. He became progressively weaker with repeated chills, fever, and sweats There was tenderness over the lower lumbar region with spasm of the erector spinae muscles and limitation of motion Radiographs showed destructive changes in the interarticular facets of the lower lumbar vertebrae on the right, most marked between L4 and L5, the psoas shadow was distorted on the right side, ballooning out inferiorly, suggesting abscess formation. Drainage of a huge prevertebral abscess was followed by recovery. *Brucella abortus* was isolated from the pus The wound healed after several months. A year later low back pain recurred A left psoas abscess was found which yielded staphylococcus and no *Brucella* Following this he recovered completely.

Chronic *Brucella* spondylitis without suppuration, leading to formation of bone spurs, may occur alone or accompanied by other joint involvement, and usually with fatigue and malaise. Figure 23 (p. 213) shows radiographic changes in the spine, associated with degenerative changes in the ilium and femoral head, in a 50-year-old farm wife, whose symptoms were controlled by *Brucella* vaccine. This type of spondylitis apparently is common in regions where chronic *Brucella abortus* infections are predominant Kulowski's case [411] is illustrated in Fig. 30.

Gautier [269] stated that pain usually was severe and most often localized in the lumbar region On radiologic study one or more vertebrae sometimes showed irregularity of the border, excavations of the bodies, and rarely osseous erosion. At times abnormal clarity of the intervertebral discs was noted.

Spondylitis closely simulating Pott's disease was reported by Archer [27] Marietta [482] reported an instance of meningeal and bone involvement closely simulating tuberculosis

Sandstrom [560] in 1937 reviewed 29 cases of spondylitis In 20 the lumbar region was involved, in 4 the dorsolumbar, in 4 the dorsal, and in 1 the cervical region He called attention to the destructive processes in intervertebral discs and vertebral bodies

Bishop [62] stated that localization in the spine may occur in any phase of the disease but is more common in the convalescent period *Brucella* of all three strains had been found in the 56 cases

reviewed. The lumbar region was most often involved, accounting for 40 cases, the thoracolumbar in 10 cases, thoracic 4, and cervical 2 In his own case of *suis* infection there was lumbar and



Fig 30 Brucellosis of vertebral column, with involvement of third, fourth and fifth lumbar vertebrae, showing partial destruction of intervertebral discs Healing stage (After A Steindler Courtesy of Dr J Kulowski)

cervical localization He quoted Serio as stating that osteomyelitis with suppuration and occasionally abscess formation occurs in the acute case, and bone spurs, usually on the anterior surface of the bodies, in the chronic form. The changes most often noted were calcification of the vertebral body, with a characteristic zone of sclerosis beginning at the site of the original focus, instead of the decalcification usually seen in tuberculous processes. The entire body and the processes may become involved In some only an angle of the vertebral body was involved, occasionally any or all the surfaces *In others it was confined to the disc with*

narrowing of the intervertebral space, rarely by more than one-half. The contour usually was preserved and nearly always sclerotic or irregular. Rarely were the articular facets involved. Bony fusion between the bodies was commonly seen. There was pain, of gradual or sudden onset, constant in nature, intense, with spontaneous exacerbations or precipitated by coughing or movement, frequently radiating along nerve trunks (p. 231). Vertebral rigidity with localized or diffuse muscle spasm was noted. Abscess formation was not as common as in tuberculosis, extension to paravertebral tissues occurring in 12.5 per cent.

Phalen, Prickman, and Krusen [582] reported 3 cases of spondylitis attributed to *Brucella* infection because of remittent fever, local signs and symptoms of spondylitis, high sedimentation rate, and blood agglutinins against *Brucella* in high titer. There was further evidence through negative exclusion in that physically induced hyperpyrexia had not been effective in control of the symptoms of the common forms of atrophic or hypertrophic spondylitis, in which the organisms of brucellosis are not the causative agent; whereas *Brucella* infections in general had yielded satisfactorily to physically induced hyperpyrexia in patients without bony lesions previously treated. In 2 of the 3 cases there were destructive lesions of the spinal column and in 1 clinical signs and symptoms of acute spondylitis without any significant bony changes All 3 patients recovered following fever therapy, with demonstrable repair of the bony lesions in 2 cases.

A case of brucellosis showing vertebral lesions was reported by Herson [334] The patient had had an injury to the spine five years before The author has repeatedly noted localized pathologic processes in parts previously traumatized (pp. 267–270).

Di Rienzo [175] stated that infection of the vertebral column may begin in the body of the vertebra, in the epiphysis, or in the disc The resultant changes may produce anything from a widespread spondylitis to a highly localized necrosis Radiographs of various patients shown in Figs 31 and 32 illustrate some of the changes ascribed by him to this process. Figure 32 shows extensive destructive process in the bodies of lumbar vertebrae in 1943, heal-



Fig 31 A and B Hypertrophic and destructive lesions of vertebrae (Courtesy of Dr Sabino Di Rienzo, Cordoba, Argentina)

ing three years later. In this patient there were high fever in recurrent cycles and severe backache. Blood culture was positive for *Brucella* and blood-agglutination reaction was positive in a

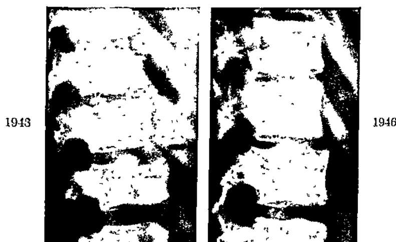


Fig 32 Destructive process in bodies of lumbar vertebrae, with healing three years later (Courtesy of Dr Sabino Di Rienzo)

1:2000 dilution. Treatment consisted of *Brucella* vaccine and roentgen therapy. He observed a large number of cases in Argentina, as did Villafañe-Lastra.[697]

Neuralgia and Neuritis

Neuralgia or neuritis may occur in the acute or chronic illness. *Neuralgic and neuritic pains* occurred in about 75 per cent of cases of acute brucellosis reported by Hughes,[369] with facial, frontal, occipital, sciatic, or other nerve distribution.

Peripheral neuritis as a late manifestation of long attacks, paralysis and atrophy, once affecting the extensor muscles of the leg, simulating the foot drop of alcoholic neuritis, and in 3 cases affecting the deltoid muscle, was reported by Hughes[369] Similar findings were reported by Westcott[706]

Sciatic neuritis was discussed by Hughes, Benedek,[50] and others. As is so usual with manifestations of *Brucella* infection, there is nothing to distinguish this condition from sciatic neuritis of other

origin, except the presence of brucellosis itself and the response of the process to specific therapy. *It may be confused with herniated intervertebral-disc syndrome of traumatic origin, or indeed may result from trauma to the vertebral column in the presence of* Brucella *infection or to partial destruction of the disc by* Brucella *infection.*

Individual Vertebrae and Intervertebral Discs

The simulation of the syndrome caused by traumatic herniation of the intervertebral disc is so very marked in some instances as to leave little doubt that *Brucella* or other infection may produce this syndrome. This view is shared by Maldonado-Allende [158] who has observed similar instances in Argentina.

Such a syndrome, i.e., sciatic neuritis with characteristic radiation of pain, increased by coughing, sneezing, or bowel movement, with typical radiographic and neurologic findings is illustrated by the following case history.

A 59-year-old farmer was incapacitated by sciatic neuritis of gradual onset and about four months duration. The pain was worse on coughing, sneezing, or straining at stool. There was numbness and tingling in the right foot.

Physical examination was essentially negative except for sensory changes in the lower leg and foot with abolition of the Achilles-tendon reflex. Routine laboratory studies were negative or within normal range. Radiographs of the lumbosacral spine and pelvis showed moderate rotary and lateral scoliosis to the right without appreciable tilting of the pelvis and loss of the normal lower lumbar lordosis. There were hypertrophic lipping on the margins of the vertebrae and narrowing of the disc between L4 and L5, more marked on the left side (Fig. 33). It seemed probable that the narrow disc was associated with herniation of the nucleus pulposus. In view of the fact that nine previous instances of sciatic neuritis had been demonstrated to be related to *Brucella* infection, routine tests for brucellosis were made. Blood-agglutination reactions were negative. The opsonocytophagic test showed a low degree of resistance. The intradermal test with *Brucella abortus* vaccine reacted strongly.

Improvement began on the sixth day following the intradermal test



A

Fig 33 A, B Hypertrophic lipping of lumbar vertebrae and narrowing of disc between L-4 and L-5


C
B

That night he slept without opiates or sedatives for the first time. Within two weeks he walked without a cane and required only an occasional mild analgesic. Pain disappeared in eighteen days at which time he was able to resume his work in the hayfields. The phagocytic index rose to a high level following the skin-testing dose of vaccine. No treatment was necessary.

There was a history of abortion in his cattle about three years previously and he had come in contact with infected animals and their products of conception at various times during his lifetime as a farmer.

Among 9 other patients with sciatic neuritis associated with brucellosis there were 8 males and 1 female, all adults. They had suffered various degrees of crippling illness for periods ranging from a few weeks to several months when first seen. In most of them the diagnosis of brucellosis was not at first evident; none exhibited high fever or other evidence of acute illness. The diagnosis had simply been the symptomatic one, i.e. *sciatica*. Diathermy and other means of treatment had afforded partial relief in some. Following realization that the syndrome was apparently referable to *Brucella* infection or allergy, *Brucella* vaccine therapy was employed, with recovery in all. (See page 449)

NEUROLOGIC MANIFESTATIONS

DeJong [168] pointed out that undulant fever is almost always accompanied by some nervous-system symptoms, apparently due to the action of bacterial toxin which may have a special affinity for the central and peripheral nervous systems Actual invasion by the causative organism, with resulting *encephalitis*, *meningitis*, or *myelitis* and focal localization resulting in aphasia, hemiplegia, hypertrophic pachymeningitis, muscular atrophies, paresis, and transverse myelitis were described as of occasional occurrence. *Spinal fluid* usually showed increased pressure, pleocytosis, increased albumin, and decreased glucose and chlorides

The same author reviewed the literature prior to 1936 and quoted the following examples of neurologic involvement. meningo-encephalitis, with fatal termination,[308] hemiparesis with aphasia, with recovery,[154] meningo-encephalitis, with recovery;[455]

meningo-encephalitis with paraplegia;[174] meningo-encephalitis with recovery,[609] pachy- and leptomeningitis, with death;[513] meningitis and a permanent transverse myelitis,[535] meningo-encephalitis,[59] all proved by culture of spinal fluid or of tissue at autopsy. Many other cases involving the nervous system have been reported.[54, 55, 81, 108, 156, 378, 412, 522, 575, 576, 581, 583, 590, 597, 637, 658]

The possibility that epileptiform convulsions may result from cortical irritation due to localized *Brucella* infection or allergy must be considered in view of the following experience:

A 61-year-old woman had two acute attacks of brucellosis in 1932 and 1933, three months apart Each attack had been ushered in by a chill and epileptiform convulsions, and there was only partial recovery between attacks After the second convulsive seizure edema of the ankles had been noted and she had complained of soreness in thigh and calf muscles and in knee joints. She had a severe colitis, with obstinate constipation, marked abdominal distention, and borborygmus All 28 teeth had been found to be abscessed and had been removed, with no improvement.

She was first seen in September, 1933, six months after the second convulsive seizure, because of a steady downhill course, with progressive weight loss and prostration She was bedridden Pallor was marked although anemia was moderate Complete study was negative except for the anemia, abdominal distention, poor visualization of the gallbladder, and low-grade fever *Brucella* agglutinins were absent Culture of aspirated bile for *Brucella* was negative Recovery followed institution of *Brucella abortus* vaccine therapy and seemed to be aided by use of 6-meter diathermy through the biliary tract She remained well for nearly three years but then had mild recurrence of symptoms referable to brucellosis whenever resistance to *Brucella* infection decreased and sensitization increased following neglect of intermittent vaccine therapy Seizures of petit mal type were frequent, with an occasional generalized convulsion at such times Electroencephalograms (Fig 34) made by Dr Joseph Hughes in 1943 and 1944 showed epileptiform patterns *He concurred in the belief that the seizures and* the encephalographic changes were ascribable to her chronic *Brucella* infection Neurologic examination was negative on both occasions

The patient is still active and fairly well at the age of 78 but is

That night he slept without opiates or sedatives for the first time Within two weeks he walked without a cane and required only an occasional mild analgesic. Pain disappeared in eighteen days at which time he was able to resume his work in the hayfields. The phagocytic index rose to a high level following the skin-testing dose of vaccine. No treatment was necessary.

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Frontal headache persisted. Two months following discharge he was readmitted to the hospital because of recurrent fever, headache, vertigo, nausea, and vomiting. There had been tinnitus, diplopia, and unsteadiness on walking during the two weeks before admission. On this admission neurologic examination showed unequal pupils, an alternating convergent strabismus, weakness with external rotation of the right eye and slight weakness of the left, neuroretinitis with blurring of the disc margins, slight elevation in the nasal half of the disc, and fine capillary hemorrhages bilaterally. Tendon reflexes were normal; abdominal reflexes were not obtained. There was a positive Oppenheim on the left, slight nuchal rigidity, a slight Kernig sign bilaterally but no Brudzinski sign, a coarse tremor of the hands on extension, increased with intentional movement, and no definite ataxia. Repeated blood cultures were negative. Spinal fluid was under pressure of 180 mm, with 63 cells per cu. mm, all small lymphocytes. Globulin was 4 plus, total protein 109 per 100 cc. Simultaneous blood and spinal fluid examination showed sugar content of 108 and 22 mgm. per 100 cc respectively. Four days later there were 200 cells per cu mm. of spinal fluid, two-thirds of which were polymorphonuclears. No organisms were found on direct smear, agglutination tests with the *Brucella* group were negative, and no growth was obtained on cultural study However, special cultures on liver infusion broth under tension of 10 per cent CO_2 produced a small Gram-negative bacillus which was agglutinated by *abortus* serum in a titer of 1,640 The organisms could be made to grow on blood agar plates and liver infusion plates under CO_2 but would not grow in air. During the first ten days in the hospital temperature rose to 100° F daily, following which it did not exceed 99.5° F. On September 28 and October 3 he was given intravenous injections of polyvalent anti-*melitensis* and *abortus* serum, Mulford There was some subjective improvement, headache, nausea, and diplopia diminished. He was discharged on October 21 without medication Three months later he was reported to show moderate improvement He had gained 12 pounds and was out of bed for a few hours daily

The insidious onset of *Brucella meningitis* or *meningo-encephalitis*, the tendency to relapse, and the absence of any early neurologic physical findings referable to the central nervous system are

dependent upon intermittent *Brucella* antigenic therapy and treatment of the anemia for relative freedom from recurrent cerebral and systemic manifestations.

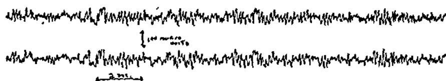


Fig. 34 A Electroencephalogram (from above downward, right frontal, left frontal and transfrontal bipolar leads). October 13, 1943 Epileptiform patterns

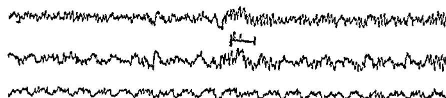


Fig. 34 B. Same patient (right frontal, left frontal and bipolar frontal leads). January 22, 1944. Similar patterns

Meningitis and Encephalitis

Meningo-encephalitis in a patient under his own observation was reported by DeJong.[168]

A farmer aged 27 was admitted to hospital on April 6, 1934, complaining of weakness, fatigue, frontal headache, generalized aches and pains, constipation, nervousness, anorexia, frequency, and nocturia of three months duration. Evening chills followed by temperature elevations from 100 to 102° F had been occurring almost daily, with profuse sweating Epitrochlear and axillary lymph nodes were enlarged There were no abnormal neurologic findings. Leukocyte count was 5,000 per cu. mm. with 60 per cent lymphocytes and 29 per cent polymorphonuclears, 10 per cent monocytes, and 1 per cent eosinophiles Blood-agglutination reaction was positive in a dilution of 1·320 The opsonocytophagic reaction was marked in 94 per cent of the cells and moderate in 6 per cent.

It was believed that his illness was subsiding and he was discharged.

with slight drooping of the right corner of the mouth, tremor of the tongue, lagging of the right side of the soft palate, and hyperactive abdominal reflexes were noted An electroencephalogram on June 18, 1943, showed short bursts of abnormal slow waves scattered over the frontal and parietal areas, somewhat suggestive of epilepsy but consistent with the neurologic and clinical evidence of encephalitis

On July 12, 1943, after a period of steady improvement during which time the ankle clonus had disappeared and other neurologic signs were lessening, there was a mild recurrence of signs and symptoms of encephalitis Temperature had been not over 99 2° F. between attacks but then ranged from 99 6 to 99.8° F. with the onset of vertigo, nausea, headache, and vomiting, with recurrence of marked right-sided ankle clonus There was subjective and neurologic evidence of improvement within twenty-four hours following the reinstitution of sulfadiazine therapy, temperature ranging not above 99 2° F, ankle clonus lessening, and headache, nausea, and vertigo abating. Electroencephalogram was repeated on August 16, 1943, and showed lessening of the abnormal wave patterns (Fig 35)

Throughout the acute illness there had been a leukopenia with relative lymphocytosis, a slightly elevated or normal sedimentation rate, and moderate normocytic anemia. Lumbar puncture was not done during the acute illness nor during the recurrence four months later. On August 6, 1943, about two weeks following recovery from the mild relapse, lumbar puncture showed a clear fluid, not under pressure, no microorganisms with Gram stain, and 1 white cell per cu mm. Chemical examination showed slightly increased protein content, Fehling's solution was reduced No growth of microorganisms was obtained Cultural examination of blood, undertaken during the acute illness, was negative She was able to return to her work in September, 1943

In January, 1947, this patient showed few sequelae Moderate atrophy of the gastrocnemius muscle persisted She still had episodes of fatigue, malaise, and low-grade fever. gradually lessening in degree and duration Several cautious attempts to bring about desensitization and to induce greater immunity had been made during the three and a half years following the acute illness but were abandoned because of unfavorable allergic reactions which reproduced some neurologic symptoms

In March, 1948, following a moderately severe attack of epidemic influenza, marked drowsiness and lethargy supervened immediately

especially noteworthy. Although cultural proof was lacking there seemed little doubt as to etiology in the following case:

A 29-year-old registered nurse, engaged in laboratory procedures which included the handling of live cultures of *Brucella abortus*, developed a series of mild grippe-like attacks of two to three days duration in February, 1943. Chief complaints were malaise, fever ranging from 100 to 101° F., unilateral stiffness, and lameness of legs and wrists Between the febrile episodes there was fatigue and general ill feeling, with an average afternoon temperature of 99.6° F. Four such attacks occurred between February and April, 1943. She remained ambulatory throughout.

On April 7, 1943, she developed stiffness and lameness of the neck with bilateral swelling and tenderness of the anterior cervical lymph glands which continued for three days At that time an acute illness supervened with fever ranging from 99 to 104° F., marked prostration, severe occipital headache, lameness and stiffness of the right side of the neck, and a semistuporous state. There was no nuchal rigidity, neurologic examinations were entirely negative. The acute illness subsided apparently in response to sulfadiazine. Low-grade fever continued for fifteen more days. On April 16, 1943, the ninth day of the acute illness, she complained of soreness of the right gastrocnemius muscle with subsequent slight swelling of the posterior aspect of the leg, from knee to ankle, apparently due to myositis. This subsided and was followed by phlebitis in the same extremity, with slight pain and moderate swelling, this process subsided almost completely within ten days

Marked swelling, tenderness, and pain in the right leg—apparently due to extension of the thrombophlebitis—recurred on May 27, 1943, during convalescence following undue exertion By the middle of June, 1943, pain had lessened but swelling of the foot and ankle continued and contracture of the tendo-achilles was evident. Blood agglutination with *Brucella abortus* was positive in a 1 40 dilution of the serum during the acute illness Opsonocytophagic test showed moderate resistance

Neurologic signs were first noted on June 17, 1943, during convalescence, more than two months after the onset A markedly sustained right-sided ankle clonus, paresis of the right quadriceps femoral group, markedly hyperactive knee jerks, paresis of the right facial group

rington, had had recurrent illnesses, all with evidence of encephalopathy. The onset in one was in October, 1946, in the second in February, 1947, and in the third in April, 1947. All had fever, intense headache, somnolence, prostration, 1 had mild stupor, 2 had nystagmus and diplopia with each attack; 1 had recurrent slurred speech and loss of upward gaze and convergence One had gastroenteritis at the onset Two had anterior cervical adenitis None had positive cultures of blood or spinal fluid, or blood-agglutination reactions Sedimentation rates and blood counts were not significant. Heterophile antibody reactions were absent One had a previous history of brucellosis when agglutinins had been present All had positive skin tests and low phagocytic indices. All responded, clinically and serologically, to *Brucella* antigens, with characteristic exacerbations of symptoms if reaction-producing dosage was employed inadvertently. They were able to return to work within three weeks after treatment with a *Brucella* antigen. One relapsed and responded favorably to streptomycin and sulfadiazine combined. A common origin was suspected but could not be traced. None were engaged in laboratory work nor were they caring for known cases of brucellosis The one whose acute symptoms developed in April, 1947, might be suspected as a carrier, in view of her previous history, but such status was not demonstrated. The cases are quoted not as proved instances of *Brucella* encephalitis but as examples of the relative frequency of central–nervous-system manifestations in patients suffering from recurrent brucellosis ♦

Roger, Pieri, and Bouet [585] reported a case of meningo-encephalitis with negative culture and positive agglutination reaction as probably attributable to *Brucella* infection Spinal fluid contained 160 cells per cu. mm , 80 per cent of which were lymphocytes The patient recovered after repeated attacks.

Atypical meningitis, with neurologic signs appearing late in the course of the illness and no early evidence of localization in the central nervous system, is illustrated in the case reported by Poston and Smith.[540] *Brucella abortus* was recovered from the

following subsidence of fever. She complained of severe headache and photophobia. Ankle clonus on the right and markedly increased bilateral tendon reflexes were elicited. Eye grounds showed venous

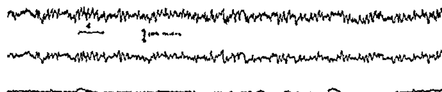


Fig 35 A Electroencephalogram (right, left and transfrontal leads) June 18, 1943 Short bursts of abnormal slow waves.

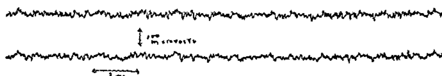


Fig 35 B. Same patient, August 16, 1943. Lessening of abnormal wave patterns

engorgement. Spinal fluid was under normal pressure and showed no abnormalities. There was gradual lessening of signs and symptoms over the next few days It was thought that this was an anamnestic allergic reaction in tissues previously sensitized by an unrelated infection. (See pp 377 and 426)

Another instance of probable laboratory infection followed by central-nervous-system manifestations occurred in a 27-year-old bacteriologist Chronic illness with fatigue, muscular incoordination, drowsiness, and low-grade fever had continued for five years, with occasional bouts of high fever, vomiting, diarrhea, and prostration. Drowsiness was extreme, at times to the point of stupor. Neurologic signs and spinal-fluid findings were absent but the diagnosis of brucellosis and low-grade encephalitis had been established on the basis of serologic studies, agglutinins against *Brucella*, and skin reaction She improved markedly following institution of *Brucella abortus* vaccine therapy in very dilute form.

Three student nurses seen in consultation with Dr. D T. Har-

rington, had had recurrent illnesses, all with evidence of encephalopathy. The onset in one was in October, 1946, in the second in February, 1947, and in the third in April, 1947. All had fever, intense headache, somnolence, prostration, 1 had mild stupor, 2 had nystagmus and diplopia with each attack; 1 had recurrent slurred speech and loss of upward gaze and convergence. One had gastroenteritis at the onset. Two had anterior cervical adenitis. None had positive cultures of blood or spinal fluid, or blood-agglutination reactions. Sedimentation rates and blood counts were not significant. Heterophile antibody reactions were absent. One had a previous history of brucellosis when agglutinins had been present. All had positive skin tests and low phagocytic indices. All responded, clinically and serologically, to *Brucella* antigens, with characteristic exacerbations of symptoms if reaction-producing dosage was employed inadvertently. They were able to return to work within three weeks after treatment with a *Brucella* antigen. One relapsed and responded favorably to streptomycin and sulfadiazine combined. A common origin was suspected but could not be traced. None were engaged in laboratory work nor were they caring for known cases of brucellosis. The one whose acute symptoms developed in April, 1947, might be suspected as a carrier, in view of her previous history, but such status was not demonstrated. The cases are quoted not as proved instances of *Brucella* encephalitis but as examples of the relative frequency of central–nervous-system manifestations in patients suffering from recurrent brucellosis. •

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spinal fluid but not from blood, urine, or feces. The patient's serum never agglutinated her own organisms. She recovered following intrathecal administration of human immune serum.

Meningitis due to *Brucella* is rarely recognized in children. Poston and Thomason[541] considered as possible *Brucella* meningitis some of the conditions diagnosed as tuberculous meningitis in which no organisms were seen on direct smear. Some cases diagnosed as influenzal meningitis in which the organisms were seen but were not cultivated may have been due to *Brucella*. They reported a case of low-grade subacute relapsing meningitis due to *Brucella abortus* in a child of 7 years, in whom complete recovery followed intraspinal injections of human immune serum.

Sanders[598] reported the first case of *Brucella* meningitis due to the *suis* species in the United States. This report was supplemented by Hansmann and Schenken,[255] who described the findings at autopsy. Symptoms and signs had at first suggested meningococcic meningitis, subacute meningitis, encephalitis, or brain tumor. *Brucella suis* was recovered from the spinal fluid. Death occurred, after a protracted illness with many remissions, from rupture of a mycotic aneurysm of the basilar artery (p 127).

Hansmann and Schenken stated that the central-nervous-system involvement may be the first and only clinical manifestations of the disease Headache, diplopia, transitory paralysis, and throbbing in the ears is of frequent occurrence in meningo-encephalitis. They considered that the organisms may be localized in the pia-arachnoid or in the larger vessels at the base of the brain for a long period of time by the feeding of a limited number of organisms, or that by the diffusion of the bacterial poisons from the localized process into the spinal fluid, or by both mechanisms, a chronic meningitis may be produced

In the case reported by the author[303] death followed a hemiplegia Autopsy revealed an extensive encephalitic encephalomalacia The patient had had symptoms referable to brucellosis for eight years before the terminal illness, with fatigue, malaise, low-grade fever, and recurrent iritis, and with occasional bouts of unexplained high fever (p 251)

Extensive metastatic encephalitis, along with thrombi of the aortic valve, was reported by Scheidegger and Stern[602] in a fatal case of brucellosis which came to autopsy. The patient was a 34-year-old man who had received a wound of the hand which became secondarily infected with *Brucella abortus*.

In the case of *Brucella suis* meningitis reported by Hartley, Millice, and Jordan[313] recovery followed a stormy course. Low-grade encephalitis apparently preceded the meningitis by four weeks. *Brucella suis* was recovered from the spinal fluid on guinea-pig inoculation but not obtained on direct culture. They compared the case with that reported by Sanders[595] and by Hansmann and Schenken,[299] in both of which the onset of meningitis was preceded by symptoms possibly due to low-grade encephalitis. In Sander's case, symptoms had existed for nine months, in their case for less than a month. In both cases the initial cerebrospinal fluid cell count was relatively high, with more mononuclear cells than would be expected with a meningitis due to meningococcus or one of the pyogenic organisms. They concluded that "a meningitis occurring in the course of proved or suspected undulant fever and showing a relatively high cerebrospinal fluid count with originally a large proportion of mononuclear cells should probably be considered, in regard to therapeusis, to be due to an infection of some organisms of the *Brucella* group." They pointed out that the causative organism in *Brucella* meningitis was most surely isolated through guinea-pig inoculation. Recovery was attributed to repeated spinal-fluid drainage and use of a *Brucella* antigen.

Encephalitis was reported in 4 cases by McCullagh and Clodfelter.[468] The outstanding symptoms were choking of both optic discs, positive Babinski sign, headache, somnolence, indications of hypothalamic and pituitary damage, diplopia, fatigue, and fever; not all symptoms occurred in all cases. In 2 instances encephalitis developed during the chronic phase of bruc[illegible]. The papilledema reported by Rutherford[593] in 3 patients brucellosis was thought to be a manifestation of enceph[illegible]

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Postencephalitic parkinsonian syndrome was noted in a 46-year-

old woman who complained of severe headaches, gradual loss of use of the right arm and hand, fatigue, dyspnea, and palpitation of gradual onset over a period of eighteen months. Examination showed a typical masklike expression; gross passive tremor of the right arm, hand, and leg; swelling of the right arm, from shoulder to finger tips; paresis and atrophy of the small muscles of the right hand Routine serologic study was negative or within normal limits. Temperature was 99 2° F. Blood-agglutination reaction was negative. Intradermal reaction to *Brucella abortus* organisms was strongly positive. The improvement that followed administration of *Brucella abortus* vaccine, given as a therapeutic test, was dramatic. Tremor of the arm and leg lessened and ultimately ceased, swelling, redness, and weakness of the arm and hand improved until she was again able to use that extremity for ordinary housework, within a period of three months. She remained under observation for two years, during which time *Brucella* vaccine was continued at monthly intervals, without signs of recurrence. There was noticeable improvement in the expression of her face. About six months after treatment was initiated she stated that her friends noticed that she looked "less sober." This case was reported [302] as an instance of parkinsonian syndrome following encephalitis, probably due to brucellosis. It bore some resemblance to the case reported by d'Amore.[150]

Peripheral neuritis with plantar hyperasthesia, apparently due to an irritative process, was reported by Gautier [249] in a patient with *Brucella* spondylitis in whom blood culture was positive.

Multiple sclerosis and brucellosis co-existed in 4 of the author's patients In only 1 was there an opportunity to observe the effects of treatment of the *Brucella* infection with *Brucella* antigens on the central-nervous-system symptoms. Improvement which could not be distinguished from possible natural remission was noted.

Neuropsychiatric complaints were found in 208 (44.3 per cent) of the 462 reactors among 7,122 school children skin tested for evidence of *Brucella* infection by Angle and Algie.[21] Headache occurred in 172 children (37 2 per cent). Neuritis (along with

joint symptoms and "aches and pains," grouped under "rheumatic symptoms") occurred in 157 children (34 0 per cent). Among 100 control students of the same age group with negative skin tests, nervous symptoms occurred in 26 (26 per cent), headache in 15 (15 per cent), and "rheumatic symptoms" in 6 (6 per cent), a statistically significant contrast.

Psychiatric manifestations have been noted by several observers.[514, 557, 567] Angle and Algie[29] reported one instance of major psychosis occurring among 154 cases of brucellosis. Calder[103] stated that the psychiatric manifestations in his observation of over 1000 patients were impressive. He mentioned insomnia, nervousness, cardiac and gastric disorders, and the "neuresthenic syndrome" (irritability, asthenia, lack of ambition, inability to concentrate, and poor memory). He stated that vague apprehensive states were not uncommon but that true episodic anxiety attacks were not encountered in his cases.

Confusion, poor memory, inability to concentrate, loss of libido, lack of ambition, and depression are frequently encountered in chronic brucellosis. It is uncertain whether it is of toxic, allergic, infectious, or psychic origin (p. 386), or whether various factors are operative. Mild psychoses appeared in 3 patients, with recovery following treatment of the infectious disease.

Using combined medical, psychiatric and experimental psychological technics in 10 patients Apter, Halstead, Eisele and McCullough[24] noted cerebral impairment in some patients which may explain many symptoms and changes in their behavioral patterns, including impairment of biologic intelligence and ego function, decrease in libido, irritability, lack of resentment, loss of former skills, inability to return to work, or to plan for the future, impoverished emotional expression and failure to establish ordinary rapport.

Evidence of brain damage was noted in the Rorschach of 1 of the author's patients studied by projective psychologic technics (p. 386), whereas Apter and his coworkers considered projective technics, including the Rorschach, as providing suggestive leads in some cases but to be non-discriminating from the standpoint

of organic brain disease, which was demonstrated by other technics in 7 of the 10. (See pages 354–355, 367–406.)

OCULAR MANIFESTATIONS

Green [271] stated: "An immense amount of work has been done in brucellosis in the past 20 years. Those who have undertaken the study of the disease, either in the laboratory or clinically have become enthusiastic about the possibilities and implications of this new malady; in fact, one is inclined to feel that some authors have allowed their enthusiasm to outrun their judgment. Evidence is accumulating, however, that some ocular maladies ascribed to other origins may be caused by brucellosis. The external ocular muscles, the cornea, the uveal tract, the retina and the optic nerve have all proved vulnerable . . . Who has not been thwarted in his most painstaking efforts to establish the cause of the chronic uveitis? Should not the ophthalmologist include in his list the possible etiologic factors of the disease that is widespread and one which has been proved to be capable of infecting almost every tissue of the body?"

He reported 4 of his own cases and cited 28 others from the literature, in 11 of which culture of the blood or spinal fluid yielded the organisms Green's series included 1 case of recurrent phlyctenular conjunctivitis and corneal ulcer, 1 of retinal hemorrhage, 1 of optic neuritis, and 1 of retinochoroiditis, clinically attributable to brucellosis The cases reviewed included one or more of each of the following conditions. corneal ulcer; iritis; optic neuritis (with or without atrophy), neuroretinitis; retrobulbar neuritis, panophthalmitis, iridochoroiditis, septic retinitis; papilledema; hemorrhagic retinitis, palsies of external ocular muscles; iridocyclitis, optic nerve atrophy, discrete myopic chorioretinitis. These lesions were associated with or independent of *Brucella* meningitis or meningo-encephalitis Although partial or complete loss of vision was not uncommon, the integrity of the globe was not affected and enucleation not indicated Many of the cases showed permanent damage, others made complete recovery, spontaneously or following various forms of treatment (p. 124).

Carpenter and Boak [118] had noted the lesions of the eye produced by *Brucella* infection and their similarity to tuberculous eye disease

Burky, Thompson, and Zepp [98] suggested that infection with *Brucella* may be the cause, or one of the causes, of periodic ophthalmia in the horse and that this infectant may play an important role in human ocular disease. *Brucella* was recovered at necropsy from the ovaries and milk of 3 mares sacrificed because of blindness due to clinical periodic ophthalmia A fourth strain was recovered from the milk of a mare with a similar ocular condition When injected into the anterior chamber of rabbits or intravenously into rabbits or guinea pigs, it produced in some but not all animals ocular inflammation resembling periodic ophthalmia in horses and chronic recurrent ocular inflammation in humans

Papilledema in brucellosis was reported by Rutherford [595] in 3 of 63 cases of undulant fever

Choroiditis was noted by Braley [80] in several cases of chronic brucellosis but he was never able to isolate the organism. He noted that the eyes healed rapidly with vaccine therapy, they also healed with no treatment but required more time. In various other cases he ascribed acute iritis, acute choroiditis, and chronic iritis and iridocyclitis to brucellosis.

Choroiditis, with or without retinal involvement, has been the type of ocular involvement most frequently seen in patients with chronic brucellosis, often occurring in those apparently well prior to the sudden appearance of the focal lesion

A 23-year-old unmarried girl was referred by Dr A B Reese for clinical and laboratory study for brucellosis as a possible explanation of a choroiditis just above the left optic disc which had developed about three weeks before (Fig 12, p 128) There was loss of the lower half of the visual field Her only other complaint was fatigue of about six weeks duration Raw milk had been used irregularly since childhood

Physical examination revealed nothing of importance except for the eye condition Blood study was not remarkable except for slight lymphocytosis (polymorphonuclear leukocytes 61 per cent, lympho-

cytes 36 per cent, and eosinophiles 3 per cent) without leukopenia. Blood-agglutination reactions with *Brucella abortus*, microscopic and macroscopic, were negative. Opsonocytophagic reaction revealed marked phagocytosis in 0 cells, moderate in 6 cells, slight in 19 cells, and none in 0 cells, a numerical index of 33. Cultural study was not undertaken Intradermal reaction to heat-killed *Brucella* organisms was rather violent. There were localized as well as systemic reactions to the skin test, with malaise, slight fever, and pain in various joints but no focal reaction. Phagocytic response two weeks after the skin test was moderate (7–9–9–0, a numerical index of 64). *Brucella abortus* bacterin was administered intramuscularly in small doses of a dilution of 1:1000 (2 million organisms per cc.), with slight local and systemic but no focal reaction. The ophthalmologist noted improvement about four weeks following the initial intradermal vaccine. Treatment was continued at weekly intervals for three months, during which time vision improved moderately and the phagocytic reaction increased to 13–7–5–0, a numerical index of 77. Varying degrees of leukopenia and relative lymphocytosis were found during this period Fatigue lessened gradually. The ocular process had become quiescent within two months. No further vaccine was given. Phagocytic indices were determined at intervals of one month, then of two to three months, for a year after vaccine was discontinued, with readings no lower than 64 and ranging as high as 94 Observation for a period of at least five years was recommended

Iridocyclitis, chronic and perhaps recurrent, *uveitis*, and *chorioretinitis*, due to brucellosis, were discussed by Krause.[415] He stated that the nodular form of iritis may predominate or an exudative iridocyclitis of low degree of activity may be present, the iritis may *simulate tuberculous or syphilitic disease*. He considered chorioretinitis as the more common of the eye manifestations. He described iridocyclitis with or without slight central retinitis or central macular lesions of the retina *Neuroretinitis* may be the only ocular lesion in the acute, severe form of brucellosis. He also mentioned *external ocular muscle palsies* as occurring in the presence of meningitis, neuroretinitis, and papilledema.

Uveitis as a complication of brucellosis has been observed frequently in epidemic areas, Amoss [13] stated. Woods and Guyton [784]

reported the study of a series of 200 patients with endogenous uveitis studied between July 1, 1939, and July 1, 1943. They performed routine tests for sarcoidosis and brucellosis. The uveitis in 15 patients was classified as probably due to brucellosis. They concluded that the actual incidence of *Brucella* uveitis is probably less than the 7.5 per cent reported in their series (p. 121).

Nummular keratitis was the subject of a report by Woods [723] (p 121) Five cases of nummular infiltrates of the cornea associated with serologic or allergic evidence of *Brucella* infection were described. In 4 of the cases the corneal process was quite similar to that described by Dimmer, Aust, and Salzman, as nummular keratitis There was no evidence suggestive of epidemic keratoconjunctivitis or other virus diseases of the cornea, except for the similar corneal infiltrates He felt that the diagnosis was strengthened by the therapeutic effect of Foshay's detoxified *Brucella* vaccine in 2 of the cases Woods suggested the term *Brucella* nummular keratitis instead of Dimmer's disease or the use of the morphologic term "nummular" alone. He speculated as to the probability that the corneal lesions may result from some minor, often unnoted, and accidental direct inoculation of the eyes.

Recurrent iritis in 3 cases and recurrent ulcer of the cornea in 1 case, associated with joint involvement in brucellosis was reported by Reed and Goldfain [556] There was strong presumptive evidence that the iritis was attributable to *Brucella* infection.

The author [305] has reported few instances of ocular ivolvement. This was not necessarily due to the paucity of cases with ocular manifestations but probably to the lack of knowledge concerning the eye which prevented evaluation of the cases encountered. The ophthalmologists to whom these patients were referred treated them empirically Spontaneous improvement may have occurred or they may have responded to *Brucella* vaccine used because of other recognized manifestations of brucellosis.

A 26-year-old woman, referred for diagnostic tests, had had recurrent attacks of keratitis and conjunctivitis confined to the right eye for four years Attacks were accompanied by severe pain, headache,

tearing, and progressive loss of vision, with partial remissions She also complained of weakness, mental confusion, joint and muscle pain, headache, and vague gastrointestinal symptoms. She was afebrile, but there was a history of chills and fever three or four years previously.

She had drunk raw milk for many years. Blood-agglutination reaction was negative, intradermal reaction positive, and phagocytic index moderately low (marked phagocytosis in 2 cells, moderate in 8 cells, slight in 12 cells, and none in 3 cells, a numerical index of 44)

Brucella abortus vaccine was administered as a therapeutic test. There was improvement both in constitutional manifestations and in the ocular condition, coincident with pronounced rise in the phagocytic index, soon after initiation of treatment. Within four months there was complete clinical recovery. There was no recurrence of keratitis or conjunctivitis during the ensuing four and a half years.

Central retinitis of a progressive nature, with a history of bilateral uveitis, keratitis, conjunctivitis, and episcleritis, recurrent for five years, occurred in a 44-year-old farmer. Tuberculin reaction had been positive and the intradermal reaction to *Brucella* antigen strongly positive *Brucella* had been isolated from feces. The eye condition apparently had been aggravated by the intradermal *Brucella* antigen, and by therapeutic doses of mixed strains of killed *Brucella* organisms and by brucellin. Cautious use of *Brucella abortus* bacterin, in dilute reactionless doses, was without effect Bizarre urine findings with occasional appearance of albumin and casts and at other times of glycosuria had been noted (p 126)

Diplopia, recurrent with each of several relapses of brucellosis, in a 35-year-old female school teacher has been reported by the author.[102] She had exhibited a cervicosympathetic syndrome with each exacerbation She was free of symptoms when seen in May, 1941, and no treatment was suggested. In September, 1946, this patient stated by letter that she had recently developed recurrence of diplopia, along with almost complete ptosis of the right upper lid, low-grade fever, and exhaustion, and that the entire illness had been ascribed to myasthenia gravis Diplopia and

nystagmus were noted in 2 patients with other evidence of central-nervous-system involvement

The following case of recurrent iritis, apparently due to brucellosis has been reported: [303]

A sailor, age 24, was sent for an opinion as to whether he was malingering, was psychoneurotic, or "really sick." He complained of headache, joint and muscle pains, epigastric distress, pronounced fatigue, and productive cough Iritis had recurred four or five times a year, together with low-grade fever, over a period of five years. He had had attacks of chills and fever lasting for three to five weeks each summer for eight years Blood-agglutination reaction was negative, cutaneous reaction was positive, and the phagocytic index low *Brucella abortus* vaccine was given intramuscularly with temporary improvement of the subjective symptoms The iritis continued to recur until the vaccine was given intravenously. This was followed by a high phagocytic response and freedom from the attacks for several months Artificial fever therapy was planned but, because of the exigencies of the service, was not carried out. He was discharged from the naval service with a diagnosis of chronic brucellosis

Three months later his family reported that he had had another attack of iritis, that there had been several severe attacks of vertigo, during one of which vision was much reduced, and that twice he had stumbled and fallen He complained of severe headache, usually lasting a few minutes and accompanied by stiffness of the neck Sharp pain developed in the left frontal region, and about four days later his right leg became weak, with a tendency to limp He had difficulty in concentrating On March 20, 1942, he had a sudden right-sided hemiplegia and was admitted to hospital His right pupil was slightly larger than the left, both reacted to light, and there was a questionable degree of choking of the left optic disc The spinal fluid on April 3, 1942, was under 260 mm of pressure and was clear with 33 white cells (85 per cent lymphocytes) and 119 mgm of total protein per 100 cc. On April 9, 1942, a biopsy cannula was passed into the left frontal lobe through a burr hole which brought forth a soft, reddish-brown granular tissue Operation was discontinued and the patient died the same day Histologic examination by Dr H R Wahl showed extensive acute and chronic encephalitis involving the pons and the

region of the left internal capsule, with a well-marked cufflike accumulation of monocytes and polymorphonuclear leukocytes in the perivascular spaces.

Nummular keratitis and iritis occurred in a patient referred by Dr. Max Goldschmidt for clinical and laboratory study because of the suspicion of brucellosis as the etiologic factor:

A 29-year-old male importer and dresser of animal hides and hair developed iritis and keratitis of the right eye which persisted for about six weeks before the other eye became involved. General physical examination and laboratory study had been negative except for slight increase in sedimentation rate.

The patient was born in Germany where his family had kept goats. He shared in the care of the animals and helped his father in processing untanned animal skins. He had had an infection of one finger following laceration by goat hair, attended by inguinal and axillary adenitis, about eight years before.

Microscopic blood-agglutination reaction was partial in a dilution of 1:80. Macroscopic blood-agglutination reaction was negative. The opsonocytophagic reaction showed a slight degree of resistance to *Brucella* infection, unlikely to have been acquired except as the result of infection (1–3–16–5, a numerical index of 29) Culture of blood for *Brucella* and animal inoculation were negative Intradermal reaction with heat-killed *Brucella abortus* organisms was positive. Following intramuscular administration of *Brucella abortus* bacterin the ocular condition improved, the precipitates disappeared and vision returned to normal.

Wagener [690] reviewed the subject of ocular brucellosis. It is becoming recognized that *Brucella* infection must be considered along with tuberculosis, syphilis and other infection as a possible incitant of obscure ocular disease

EAR, NOSE, AND THROAT

Sinusitis, usually frontal, but also involving antra and other accessory sinuses, is a frequent concomitant of brucellosis, as would be expected because of the relative frequency Rarely has cultural evidence of *Brucella* as an etiologic factor been presented. Failure

of recovery from sinusitis by the usual methods, until inception of specific treatment for brucellosis, was noted in 6 patients. Recurrence of symptoms with repeated relapse of brucellosis added some grounds for considering the sinusitis to be causally related.[142, 337] Cody[142] made similar observations. Hirsch,[336, 337] after reviewing the literature in 1935, concluded that affections of the paranasal sinuses probably occur in acute and chronic brucellosis.

Epistaxis occurs frequently in brucellosis, in the acute illness often suggesting typhoid fever, but also in the chronic illness, with greater frequency than is likely to be accounted for by pure chance It has been mentioned but rarely in the literature. A young farm laborer had had frequent profuse epistaxis for nine years, in irregularly recurring cycles, before an acute, severe attack of acute brucellosis supervened. Blood agglutination with *Brucella abortus* was positive in a 1:2500 dilution. During the chronic illness which reappeared following the acute exacerbation, epistaxis persisted until specific therapy was begun; it then ceased for five years, recurring during a stage of mild relapse or reinfection.

In several other patients, recurrence of nosebleed served as one index of recrudescence of *Brucella* infection. Usually no pathologic changes are noted but ulceration may occur. In one patient, in whom epistaxis had never occurred, there were complaints of fatigue, headache, weakness, and pain in one side of the nose. There was a greyish, thin, membrane-like patch on the mucosa over the inferior turbinate which remained stationary while the patient was under observation Soon after vaccine therapy was begun all symptoms and signs disappeared. Jordan and Borts[354] reported nosebleed and nasal ulceration (not necessarily coexisting) in several of 20 patients in Iowa who were suffering from *Brucella melitensis* infections Hughes, however, observing severe *melitensis* infections in Malta, noted epistaxis in only a few early cases.

Pharyngitis occurring in brucellosis shows little to distinguish it from pharyngitis of other origin. A patient who had had recur-

rent chronic brucellosis for five years, developed severe pharyngitis with intensely reddened and swollen mucosa as part of an unusually severe reaction to *Brucella* vaccine. It persisted for five days after the febrile reaction had subsided.

Pharyngitis was noted in childhood brucellosis of rapid onset by Paterson and Hardwick[527] (p. 85). Cody[142] stated that the mucosal lesions of the pharynx and larynx may resemble those of tuberculosis and syphilis. Hirsch[336] described pharyngitis in 2 cases of brucellosis. Lieberherr[440] reported pharyngitis and laryngitis in 11 of 24 cases of brucellosis.

Chronic purulent otitis media, proved by culture, has rarely been reported[303] The following case may represent otitis media of *Brucella* origin:

A 40-year-old woman complained of fatigue, joint and muscle pains, low-grade fever, and a bilateral chronic purulent otitis media of several months duration Culture of the discharge revealed a Gram-negative bacillus or coccobacillus which could not be positively classified as *Brucella* but which had its essential morphologic and staining characteristics Blood-agglutination reaction with *Brucella abortus* was negative, intradermal reaction positive, and phagocytic index low The dramatic and rapid cessation of the discharge and healing of the drums following therapeutic trial injections of *Brucella abortus* vaccine coincident with rise in the phagocytic index, after other measures had failed, suggested the likelihood that the middle-ear infection was of *Brucella* origin No local therapy or other treatment was used With recovery from the ear infection, the subjective complaints—fatigue, joint and muscle pains—disappeared

Acute purulent otitis media occurred in a 4-year-old boy reported by Cody,[142] in the presence of fever, arthritis of knees and elbows, and scattered ulcers over the buccal mucosa and lips Blood-agglutination reaction was positive in a titer of 1 640 There was slight thick purulent drainage after incision of the drums.

Mastoid infection with granulopenia in brucellosis was reported by Oppenheimer, Dennis, and Badeen[illegible]

Tonsils may serve as foci of infection, perhaps determining ear, nose, and throat infection. Carpenter and Boak[117] reported isolation of *Brucella abortus* from 8 of 56 pairs of surgically removed tonsils. Fetterof[215] reported *Brucella* infection complicating tonsillectomy.

Nerve deafness, with disturbance of both the cochlear and vestibular branches, attributed to degenerative changes in the nerve-ganglion apparatus and probably due to circumscribed meningitis, occurred in the course of a severe acute brucellosis in a 32-year-old farm woman, reported by Hirsch[337] Bilateral tinnitus had directed attention to the ear condition. In a review of the literature he referred to Hvidt's report of bilateral impairment of hearing for high-pitched tones and "slight changes in the spinal fluid"; to Bergmark's case of a meningo-encephalitis caused by *Brucella* infection, with impaired hearing of central origin in whom postmortem examination showed round cell infiltration especially in the region of the Sylvian fissure, to Videbech's case of bilateral acoustic neuritis with impaired reception of high-pitched tones and slight anomalies of the vestibular apparatus, to Cantaloube's observation of impaired hearing in 20 per cent of all cases of brucellosis; to Saquépée's report of impairment of hearing, and to reports of others of impaired hearing due to nerve involvement, some with definite evidence of meningitis or encephalomeningitis, some with various other neurologic disturbances and labyrinthine symptoms, with vertigo and tinnitus. Cody[142] stated that nerve deafness may occur as a complication of brucellosis, as with other infections

Labyrinthitis may occur in the course of acute or chronic brucellosis

DERMATOLOGIC MANIFESTATIONS

Hughes[369] rarely noted skin manifestations, mentioning pimples mistaken for the rose rash of enteric fever, sudamina as commonly occurring, boils not necessarily related to the infection, "small temporary subcutaneous nodules on the face and extremities, lasting about a week and then disappearing sponta-

neously, never exceeding an orange pit in size," and rare subcutaneous hemorrhages.

Simpson[632] stated that in acute brucellosis a transient cutaneous eruption, usually papular, macular, or maculopapular, is a relatively infrequent finding and that the lesions may simulate the roseola of typhoid fever. Of the first 103 cases reported by the same author[628] in 1931, a macular cutaneous eruption was noted in 11 chronic cases (10.6 per cent). Kern[397] reported skin eruptions in about 11 per cent of cases. Levine, Myers, and Leggett[438] noted a maculopapular rash in 5 per cent of their cases. Sharp[620] stated that skin changes have been frequently recorded clinically but not at autopsy and that they are "largely blood vascular"; erythema multiforme was encountered repeatedly. Jordan and Borts[354] mentioned a macular rash, resembling that seen in streptococcic septicemia, in several cases of *melitensis* infections in Iowa.

Few of the author's patients with skin lesions associated with brucellosis had the advantage of dermatologic consultation and study. Descriptions therefore are rudimentary in some instances. Cultural proof of the relationship was lacking but clinical and other laboratory evidence seemed adequate. Among 247 cases of brucellosis (mainly in the chronic phase) observed between *1932 and 1941, 22 (8.9 per cent) exhibited skin lesions* while under observation. The lesions often appeared and disappeared along with other symptoms definitely attributable to recurring chronic brucellosis. In some eruptions were identical during repeated relapses and in others dissimilar.

The skin lesions fell into twelve main groups, often more than one type was present in the same patient:

1. Macular, pink or red, scattered, itching lesions, usually of forehead, temple, cheeks, and occasionally of arms and trunk, sometimes resembling scabies except for distribution and intensity of itching.
2. Maculopapular or papular eruptions, in small groups or scattered over the body, often a bright orange-red in color, occasionally



A



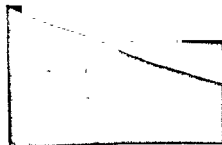
B



C



D



E



F

Fig 36 A Recurrent maculo-papular lesions of face
B [illegible]
C [illegible]
D [illegible]
E [illegible]
F Maculopapular scaling and crusting lesions of arms

with small central vesicle, sometimes resembling insect bites, sometimes herpetiform

3. Erysipelas-like lesions, in single or multiple patches, usually on the extremities; these lesions were painful, tender, and accompanied by varying degrees of constitutional symptoms and fever
4. Multiple patches of dusky, cyanotic, tender, painful nodules closely simulating erythema nodosum, of the lower extremities, usually accompanied by erysipelas-like lesions, and attended by fever and malaise
5. A diffuse erythematous rash of the entire body, including the mucous membranes of the mouth and throat, accompanied by marked constitutional symptoms, high fever, and prostration, resembling scarlet fever
6. Scaly, reddish-brown, itching lesions, usually confined to arms and wrists, sometimes resembling psoriasis
7. Crusting, seropurulent lesions, usually in small areas on arms and legs, somewhat resembling impetigo and perhaps due to secondary infection
8. Circinate and macular pink, scaly lesions, resembling pityriasis rosea
9. Papular, maculopapular, and pustular contact dermatoses with distribution corresponding to exposed areas
10. Ulcerative dermatitis
11. Purpuric patches
12. Eczematous lesions and other unclassifiable skin conditions

A fine macular rash somewhat resembling scabies occurred in 2 patients. One was a farm laborer with a protracted chronic illness, followed by a severe, prolonged, acute exacerbation which in turn was followed by low-grade fever and other evidence of chronic *Brucella* infection (p. 145). The eruption appeared on the forehead and to a lesser degree on the temples and neck, accompanied by mild itching. It was first noted during the chronic phase of the illness preceding the febrile stage; it waxed and waned in intensity until ultimate complete recovery. When *Brucella* vaccine therapy was instituted during the second chronic phase the rash reappeared with each reaction accompanying the earlier doses of vaccine. Nearly six years later, following severe

grippe, there was a recurrence of fatigue, weakness, headache, cough, and chest pain, accompanied by a coarser maculopapular rash of the cheeks and lips (Fig. 36A). This, together with the constitutional symptoms, disappeared two days after a single dose of *Brucella* vaccine.

A similar macular rash occurred during a subacute attack of brucellosis in a young man living on a dairy farm. Agglutination reaction was positive in a 1:160 dilution. The eruption disappeared with the spontaneous remission of the illness a few weeks later. A year later, during an exacerbation of brucellosis, a similar rash reappeared, this time on forehead, arms, and trunk. After the skin condition had persisted with minor fluctuations for more than six months, *Brucella* vaccine was given; the rash promptly disappeared, together with the constitutional symptoms. With a relapse of the illness two years later a dissimilar orange-red papular rash appeared on his neck and spontaneously subsided (Fig. 36B) (The fine macular rash originally presented by these 2 patients was not photographed)

Orange-red papular lesions, varying in size from 0.5 to 2 5 cm., recurred on various parts of the body in a 43-year-old man over a period of three years. Their color and texture closely resembled the intradermal reaction to *Brucella* vaccine. The skin lesions steadily subsided, along with clinical recovery, as the intradermal reaction subsided A more complete study is reported in the chapter on pathology (p 138)

A fine, maculopapular, itching eruption involving face, arms, and legs, most marked in the cubital and popliteal fossae was seen in a West Indian Negro woman of 39. It was black on chocolate-brown skin, it had appeared and disappeared during the previous year and had resisted various methods of treatment instituted by dermatologists. There was swelling of both legs, a large painful ulcer overlying the internal malleolus of the right leg, and a small ulcer in a similar position on the left, the large ulcer had been present for five years and had resisted all treatment. There was no history of syphilis blood Wassermann was negative The intradermal reaction to *Brucella* antigen was positive and was

accompanied by a flare-up of the constitutional symptoms (malaise, fatigue, and low-grade fever) and of the skin eruption, followed by marked improvement in the skin condition. Vaccine therapy was instituted as a therapeutic test; each of the earlier doses was accompanied by exacerbation of the rash and recurrence of fatigue and malaise. Gradual disappearance of the rash, as well as constitutional symptoms, occurred within six weeks. The ulcer had become more angry with each of the early reactions and then slowly healed. There was no recurrence of skin eruption, ulceration, or constitutional symptoms in the two years dur- [illegible] ervation.

[illegible] *ect bites* were exhibited by 3 [illegible] They occurred at all seasons [illegible] The patients complained of severe itching. All had positive blood-agglutination reactions and positive intradermal tests. It was noted that the skin-test reaction so closely resembled the lesions as to be indistinguishable from them In each instance the rash disappeared following the first or second dose of *Brucella* vaccine. The lesions were papular, usually about the size of a split pea, and most profusely distributed over the legs. Some were orange-red, others pink or red Scratching had converted many into crusting lesions. They had existed too long prior to specific treatment to consider the response as pure coincidence.

Erysipeloid lesions, in single or multiple patches, occurred in 7 patients. In 4 the lesions were indistinguishable from erysipelas. In 2 patients the lesions resembled erysipelas but were more elevated and nodular, somewhat resembling erythema nodosum In 1 patient the predominating lesions were characteristic of erythema nodosum, intermingled with patches closely resembling erysipelas In 1 patient the predominating lesions were obviously due to contact dermatosis of the hands, later with erysipelas-like lesions of the legs

A woman of 38 sought advice because of a scarlet patch, about 6 cm in diameter, on the lower leg Temperature was 99 6° F. Prompt response to ultraviolet light radiation was expected, however the rash

slowly spread and temperature slowly mounted, accompanied by headache, malaise, and progressive increase of fatigue which she then recalled had been recurrent for the past year. Following three intensive doses of ultraviolet light with no improvement, discrete small patches of an orange-red maculopapular eruption appeared above the original lesions in the course of the next two weeks. Blood-agglutination reaction with *Brucella abortus* was positive in a 1:80 dilution. Following the second dose of *Brucella abortus* vaccine the rash faded and disappeared and constitutional symptoms and fever slowly subsided. The patient remained well for two years, then a similar rash appeared on the same leg near the site of the original lesion There was a coincident recurrence of low-grade fever and mild malaise. Blood-agglutination reaction was positive in a 1:20 dilution. She responded rapidly to a second course of *Brucella abortus* vaccine.

Skin manifestations exactly simulating erysipelas occurred in a girl of 18 (Fig 36*C*). The appearance of dusky red, slightly elevated patches of various size on both legs was abrupt and accompanied by no constitutional symptoms. Temperature was 99.2° F. Blood-agglutination reaction was positive in a low dilution of the serum and skin test was positive. Response to sulfanilamide therapy was prompt, the tenderness, swelling, and redness lessened in twenty-four hours and disappeared in three days

A woman of 52, mother of the patient described above, was extremely ill, with fever, pallor, and prostration Multiple erysipelas-like lesions, varying in size from a dime to the palm of the hand, covered both legs from iliac crests to below the knees. Some of the lesions exactly resembled the nodules of erythema nodosum. They were hot and tender to the touch, and spread steadily, gradually changing color (Fig. 36*D*). Blood-agglutination reaction was negative. Skin test was violently positive, producing a reaction which closely resembled the original lesions on the thighs (p 352) The phagocytic index was at a moderate level, with a numerical index of 60.

Improvement closely followed the administration of sulfanilamide, fever, malaise, and prostration disappearing as the skin lesions faded Toxicity due to the drug was manifested early and *Brucella abortus* vaccine therapy was substituted, with complete recovery. A marked and sustained rise in the opsonocytophagic index occurred coincident

with clinical improvement. The right leg, which had been greatly swollen for ten years following phlebitis (p 177), steadily improved following initiation of *Brucella* vaccine treatment, swelling almost completely disappeared and she was able to discard the elastic stocking She was seen again six years later because of mild recurrence of fatigue, malaise, and low-grade fever, and moderate recurrence of swelling of the leg Phagocytic index was at a low level. She responded well to reinstitution of *Brucella abortus* vaccine treatment, clinically and serologically.

A butcher, 35 years old, suffered a sudden, painful, tender swelling of his right forearm, beginning at the wrist and rapidly spreading almost to the elbow. Temperature was 100° F. He had numerous abrasions on both hands, which had been incurred while butchering infected cattle. The skin of the involved part of the arm was hot and red, resembling erysipelas (Fig 36*E*). Blood culture was sterile. The blood-agglutination reaction was positive in a low dilution of the serum Neoprontosil, given orally, was followed by steady regression of the skin lesions, but a subcutaneous abscess appeared near the elbow. Culture of the pus yielded no organism.

A hemorrhagic, purplish-red, papular rash over the dorsum of both hands developed in a farm laborer of 50, following milking of infected cattle. The distribution was glovelike, with no lesions appearing above either wrist. The hands were swollen, tender, and painful Temperature ranged from 99 6 to 100 2° F and there was general malaise After ten days there was gradual resolution accompanied by moderate exfoliation At this time an erysipelas-like patch appeared over the anterior aspect of the right leg and a second patch overlay the knee The entire leg became swollen and painful, and there was marked tenderness in the erythematous plaques Vaccine therapy was then begun, the first dose being followed within six hours by exacerbation of the lesions of the hands and legs A second dose of vaccine with sulfanilamide was followed by improvement within a few days and then disappearance of all lesions

A scarletiniform rash, associated with high fever, occurred in a 28-year-old veterinarian in 1932. The rash was heavy, generalized, also involving the mucous membranes of the throat. It ran

an atypical course for two weeks and was not followed by exfoliation. A throat culture was negative for hemolytic streptococci Several weeks later a blood-agglutination test with *Brucella abortus* was positive in a high dilution of the serum. Green[250] later described a fleeting scarletiniform rash that developed in a research assistant who handled cultures of *Brucella*.

Lesions resembling psoriasis were encountered in 4 patients with chronic brucellosis. They exhibited almost identical, reddish-brown, dry, scaly, itching lesions involving the arms only, papular lesions with many linear excoriations were heavily interspersed. The scales were not silvery. All of these patients had had the eruption for several months in varying degrees before *Brucella* vaccine therapy was given. In all instances there was marked improvement or complete disappearance within two weeks. One patient, a farmer's wife, had repeated recurrences with subsequent relapses or reinfections with *Brucella* (Fig. 36F).

Lesions resembling impetigo were present on the arms of a 4-year-old boy The ulcerating, crusting lesions were accompanied by a few papular eruptions of the type previously described. Cultures showed no staphylococci or hemolytic streptococci. Blood-agglutination and intradermal reactions for brucellosis were positive There was no response to the usual successful methods for the treatment of impetigo, but prompt disappearance of both types of lesions followed the institution of test doses of *Brucella abortus* vaccine A few other skin affections with seropurulent discharge were noted in patients with eruptions of other types, associated with chronic brucellosis and yielding to the vaccine therapy of the apparent underlying infection

Macular and circinate lesions resembling those of pityriasis rosea were observed in 2 patients with positive blood and skin reactions and low opsonocytophagic indices They improved promptly, apparently in response to specific vaccine therapy, with a coincidental rise of the opsonic power of the white cells and disappearance of constitutional symptoms

Purpuric patches on skin or mucous membrane of various parts of the body were observed in numerous patients In some the

lesions were like simple contusions. In 7 others the spontaneous appearance of subcutaneous hemorrhage occurred with each of several relapses and ceased when clinical and serologic recovery was established.

Contact dermatoses may occur in veterinarians or others in close contact with infected animals A veterinarian observed periodically by the author over a period of sixteen years developed an erythema of the forearm and a furuncular eruption which was slow in resolution and healing, after each of several exposures to infection in cows With each there was exacerbation of fever, fatigue, headache, and joint and muscle pains from which he had suffered for several years Even in the absence of concomitant skin eruption this patient noted a flare-up of his characteristic syndrome within twenty-four hours of each exposure After he began to wear elbow-length gloves during the obstetric care of cows no further skin manifestations developed, although systemic manifestations of brucellosis continued to recur. He improved under *Brucella* vaccine therapy but resensitization or reinfection occurred at frequent intervals During periods of several months each year when he devoted his time exclusively to the supervision of race horses his response to vaccine was more complete and skin lesions did not recur.

Huddleson and Johnson [361] described a fine red macular rash and a red papular rash on the hands and arms of veterinarians who had been exposed to infected animals Itching was an outstanding symptom The rapidity with which the rash appeared following exposure (sometimes within an hour or even less) suggested that this type of lesion was an allergic response to the infected material Haxthausen and Thomsen [319] considered that the dermatitis seen in veterinarians is of allergic rather than infective origin

Weber [697] reported a case of recurrent, severe dermatitis in a veterinary surgeon, involving the arms in a bright, intensely itching erythema which was spotted with grouped follicular papules and a few bright-red and brownish vesicles. Older lesions had developed small crusts, the removal of which left sharply

punched-out, depressed points. The eruption invariably followed exposure to infected cattle and cleared up within two weeks if no further exposure occurred. If, because of the eruption on the right arm, the left arm was used in obstetric work, a similar process occurred there. The eruption did not occur if rubber gloves were worn. Itching began about thirty minutes after contact with the birth canal of the cow and the eruption appeared within twenty-four hours. The onset of the itching was so invariable as to indicate to the surgeon that he was working with contagious abortion. Patch tests, made with vaginal exudate of cows about to abort, were positive

Ulcerative dermatitis was described by Flanchik and Freyfeld [221] in 1 patient and by Zeman [738] in another:

The first case occurred in a 25-year-old laboratory technician who accidentally inoculated the skin of her thigh with a live culture of *Brucella abortus* On the same day an area of reddened, tender infiltration of the skin developed at the site of inoculation, to disappear within two days A month later there was a sudden onset of fever, headache, prostration, and marked erysipelas-like erythema of the skin of the left leg, which was swollen and tender The erythema disappeared spontaneously as did the constitutional symptoms, but a similar area developed on the anterior aspect of the leg This patch slowly absorbed, the skin assuming a bluish shade and showing softening and atrophy at the center over a period of several weeks New areas appeared for the next year, on calves, thighs, and one forearm Three of the lesions ruptured spontaneously and discharged a serohemorrhagic fluid, then healed slowly, leaving atrophic pigmented cicatrices Culture of the exudate yielded *Brucella abortus* Blood-agglutination reaction was positive in a 1 1200 dilution of the serum The lesions continued to recur for several more months, ranging in size from 2 to 9 cm One lesion was reddish purple, sensitive to the touch, with marked fluctuation at the center Another ulcerated, discharging a serosanguineous exudate, it was round, with flabby eroded borders, the bottom covered with unhealthy granulations. Treatment with an autogenous vaccine resulted in slow improvement The skin lesions showed decided exacerbations accompanying each dose of vaccine—exudate, lividity, and sensitiveness increasing and then subsiding

The second case, reported by Zeman, was somewhat similar. The patient, a woman, was acutely ill with chills, high fever, headache, vomiting, and profuse perspiration. Eleven days after the onset several dark red areas of hard infiltrations, 3 to 4 cm. in diameter, appeared on the chest and back. Pustules containing yellowish fluid, in which erythrocytes and detritus were present, developed in some of these patches. The pustules ruptured and exuded but showed no tendency to granulation. Necrosis appeared in some areas, spreading throughout the whole lesion. Necrotic infiltration appeared in the left submaxillary region, the inguinal region, and on the abdomen. The skin healed extremely slowly during four months in the hospital. There was moderate leukopenia and slight lymphocytosis; the blood-agglutination reaction with *Brucella abortus* was positive in a 1:1000 dilution.

Unclassifiable eczematous processes of long standing, clinically indistinguishable from allergic or infectious skin manifestations of other origin, occurred in several patients with chronic brucellosis and responded to *Brucella abortus* vaccine therapy, along with clinical and serologic evidence of improvement. It is possible that some of these lesions were coincidental and that improvement occurred due to the improved state of the patient's general health.

Seborrheic acne of severe degree of six years duration was seen in a 24-year-old woman. Blood-agglutination reaction with *Brucella abortus* was positive in a low titer, intradermal reaction was positive, and an opsonocytophagic test showed a moderate degree of resistance. Blood-sugar level was 180 mg. after a twelve-hour fast. The skin lesions cleared up completely following a short course of *Brucella abortus* vaccine treatment, following which the blood sugar returned to a normal range, under no dietary restriction. This was the only instance in which this type of skin lesion was encountered in a seemingly significant relationship to brucellosis.

Edema of the ankles and face was noted by Hughes, especially during convalescence from acute brucellosis. It was noted in several of the author's patients at various stages of the acute or chronic illness. At times the edema was marked, involving hands,

punched-out, depressed points. The eruption invariably followed exposure to infected cattle and cleared up within two weeks if no further exposure occurred. If, because of the eruption on the right arm, the left arm was used in obstetric work, a similar process occurred there. The eruption did not occur if rubber gloves were worn. Itching began about thirty minutes after contact with the birth canal of the cow and the eruption appeared within twenty-four hours. The onset of the itching was so invariable as to indicate to the surgeon that he was working with contagious abortion. Patch tests, made with vaginal exudate of cows about to abort, were positive.

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pressed belief that nodular vasculitis represents an entity which is not due to tuberculosis Among the author's patients, in whom definite diagnoses of acute or chronic brucellosis was established, 3 instances of erythema nodosum, 4 instances of recurrent thrombophlebitis, 1 instance of pernio, and 1 instance of panniculitis were encountered Histologic and cultural studies of the lesions were not undertaken because of lack of adequate facilities. In all cases there was response to specific therapy for brucellosis suggesting an etiologic relationship to *Brucella* infection Histologic and cultural study of similar lesions may show *Brucella* to be the etiologic factor in some instances.

THE ROLE OF TRAUMA IN REGIONAL SYMPTOMATOLOGY

Among 247 patients with brucellosis observed prior to 1941 there were 13 cases in which relatively slight trauma produced local symptoms out of all proportion to the severity of the injury. The localization of manifestations of brucellosis following trivial trauma was discussed as if it were an original observation in 1937 [299] Later search of the literature brought to light an article by Kennedy [305] in 1904 which discussed the same theory and cited examples He was of the opinion that severe localized symptoms are due to an actual deposit of organisms in affected tissues. In some cases, tissue allergy rather than localized infection seems to be the mechanism involved

Arthritis involving various joints occurred in 11 patients known to be ill with chronic brucellosis or subsequently so demonstrated, subsequent to injuries which were too trivial in themselves to explain the pathologic changes.

A 78-year-old woman fell, twisting her right shoulder, and came under observation five weeks after the injury Pain in the shoulder, marked swelling, and limitation of motion had persisted The shoulder was uniformly swollen and tender. There was no radiographic evidence of injury She gave a history of recurrent fatigue and joint and muscle pains of many years duration Blood-agglutination reaction was negative and intradermal reaction to killed *Brucella abortus* or-

face, and ankles. In a few patients the distribution was bizarre, it involved small areas of each cheek or on the eyelids, in one patient the left half of the face alone was affected, resembling



Fig. 37 A and B Edema of the face before and after initial dose of *Brucella abortus* vaccine

angioneurotic edema Edema of the upper half of the face (Fig 37) which had existed for a week in a woman with a chronic infection was noted It subsided within twenty-four hours after the first dose of *Brucella* vaccine, the second film was made two days later

Histologic studies of skin lesions are recorded on pages 138–143.

NODULAR VASCULAR DISEASES OF THE LEGS

Montgomerie, O'Leary, and Barker [496] grouped under this heading nodular vasculitis, erythema induratum, erythrocyanosis, pernio, erythema nodosum, panniculitis, recurrent idiopathic thrombophlebitis, and indurated cellulitis and ulceration secondary to chronic venostasis, of nontuberculous origin. They ex-

with recurrent pains in various joints and muscles, and fatigue. He had papular, itching eruption on face and neck along with his systemic manifestations. There was swelling over the anterior aspect of the knee joint and tenderness over the head of the tibia The intradermal reaction to *Brucella* vaccine was positive, the skin reaction was accompanied by an exacerbation of the skin eruption and of lameness of the injured knee and of one wrist joint, not previously involved *Brucella abortus* vaccine, begun as a therapeutic test, also caused moderate reactions and exacerbations of joint pains and lameness, especially in the affected knee joint. After the third dose of vaccine there was definite improvement in the knee and also in the constitutional symptoms.

Hayes [320] reported a similar instance. A young laborer recovered from a strained knee joint in two weeks, eight months later the lameness and swelling reappeared although there had been no further injury. The blood-agglutination reaction with *Brucella abortus* was negative, the skin test was strongly positive Reaction to the intradermal test dose of vaccine was accompanied by sharp focal reaction in the joint, then by prompt subsidence of the joint swelling and lameness.

Low-grade osteomyelitis of the carpal bones was found in a laborer of 61 (p 216). This patient suffered a minor injury which was followed so closely by signs and symptoms referable to *Brucella* infection as to leave little doubt as to its etiology, in retrospect. Radiographs showed a destructive process of the entire carpal region (Fig 26). An award under the Workmen's Compensation Law for 50 per cent loss of function of the wrist and hand had been made before the probable relationship between *Brucella* infection and the progressive infection of the bones of the wrist was suspected Vaccine therapy was not instituted until a year after the injury had occurred and during this time there had been no spontaneous improvement. Within two months of the institution of vaccine therapy there was about 50 per cent improvement in swelling, tenderness, and function.

Persistence of swelling of the foot was noted in a woman of 56 after the healing of a fracture of the navicular bone The foot

ganisms positive. The shoulder condition returned to normal soon *after the institution of test doses of Brucella abortus* vaccine

A woman of 58 suffered complete crippling of the right shoulder of six months duration following a very slight strain occasioned by reaching up to the head of her bed to put out the light, in October, 1937. She consulted the author in April, 1938, carrying her arm fixed to her side, suffering intense pain and with virtually no motion in the affected joint. During a month of hospital care she had had short-wave diathermy with no improvement. All laboratory and physical examination was negative or within normal limits, including blood-agglutination reaction and intradermal reaction with *Brucella* organisms. Radiographs showed periarthritic changes (Fig. 20). There was a history of severe anemia, thought to be pernicious, which had been kept under control by parenteral liver extract. Her husband maintained a large herd of cattle in which contagious abortion had been discovered several years before and she had used the raw milk and cream regularly. She asked why she could not have *Brucella* infection, in spite of negative laboratory evidence. She was told that skin tests occasionally were negative even in the presence of positive agglutination reactions and positive cultures and that a therapeutic trial of *Brucella* vaccine would be justified under the circumstances. There was local, focal, and general reaction to the first intramuscular dose of *Brucella abortus* vaccine, followed within a few days by improvement in the shoulder. About 90 per cent of the range of motion was restored within the next six weeks, during which time pain had virtually disappeared. (Allergic reaction to the intramuscular use of *Brucella* vaccine is unusual in the presence of negative skin reaction)

Similar instances were encountered in industrial cases

A 25-year-old laborer complained of a swollen, painful knee joint when he was first seen in April, 1940 He had been injured a month before, when the steering lever of a tractor struck a glancing blow on his knee. He had considered the injury to be trivial and had continued to work until swelling, lameness, limitation of flexion, and pain on walking had begun a week later. The condition had subsequently improved, then flared up at intervals of a few days to a week or more. He gave a history of having felt mildly ill for the past several months,

with recurrent pains in various joints and muscles, and fatigue. He had papular, itching eruption on face and neck along with his systemic manifestations. There was swelling over the anterior aspect of the knee joint and tenderness over the head of the tibia The intradermal reaction to *Brucella* vaccine was positive, the skin reaction was accompanied by an exacerbation of the skin eruption and of lameness of the injured knee and of one wrist joint, not previously involved *Brucella abortus* vaccine, begun as a therapeutic test, also caused moderate reactions and exacerbations of joint pains and lameness, especially in the affected knee joint After the third dose of vaccine there was definite improvement in the knee and also in the constitutional symptoms.

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Persistence of swelling of the foot was noted in a woman of 56 after the healing of a fracture of the navicular bone. The foot

had remained swollen, red, and painful, necessitating the continued use of crutches. Blood-agglutination reaction with *Brucella abortus* had been positive on several occasions during the previous two years when she had complained of recurrent cystitis and other symptoms. Vaccine therapy had been refused and the condition of the foot remained the same for another three months At the end of this time a trial of *Brucella abortus* vaccine was followed within a month by complete recovery.

GLANDULAR SYSTEM

Mastitis has been observed infrequently in the female and rarely in the male breast among the author's patients Hardy, Jordan, and Borts [274] stated that the not-infrequent occurrence of mastitis in undulant fever suggests specific infection localized in breast tissue. Haden and Kyger [243] reported pain and swelling of the breasts in a 14-year-old white boy in whom symptoms referable to brucellosis began in 1930. With each of six relapses during the next sixteen years there was recurrence of pain and swelling of the breasts which finally became hypertrophied. *Brucella* has been isolated from breast abscess.

Thyrotoxicosis was noted in several patients with chronic brucellosis. It was uncertain whether the condition was simply coincident with or intensified by *Brucella* infection or whether its development was a psychosomatic manifestation incident to long illness.

A 60-year-old widow had been advised to have thyroidectomy because of a rapid, irregular pulse, loss of weight, nodular enlargement of the thyroid, and a basal metabolic rate of +60 She also complained of fatigue, malaise, tremor of the fingers, and severe unilateral brachial neuritis, recurrent over the past several years. There were signs of early cardiac decompensation Blood-agglutination reaction with *Brucella abortus* was positive in a 1 80 dilution and skin test with heat-killed *Brucella abortus* organisms was strongly positive, with intensification of existing symptoms. The cardiac condition improved under the influence of digitalis but other symptoms persisted Therapeutic test doses of *Brucella abortus* vaccine produced moderately severe re-

actions, with aggravation of neuritic pain, malaise, and fatigue, ultimately followed by complete recovery. Basal metabolic rate returned to normal range The thyroid gland markedly lessened in size although the nodular consistency remained during a five-year follow-up.

Curtis and Kredel[153] reported an instance of "undulant fever complicating toxic goiter." It is noteworthy that this case was considered to be one of undulant fever complicating toxic goiter, rather than of toxic goiter associated with or complicating undulant fever. Blood culture yielded *Brucella abortus* and agglutinins against *Brucella* were present in high titer Glycosuria was present (p 181).

That endocrine glands are directly or indirectly affected by brucellosis is not surprising in view of the tendency of the organism to invade virtually all tissues of the body or to cause allergic manifestations in them Hyperglycemia and glycosuria are discussed elsewhere (p 181). Abscesses of the pancreas, involvement of testes, ovary, and other internal secreting glands, due to or complicating *Brucella* infection, must necessarily give rise to various evidences of endocrine dysfunction, many of which are mistaken for primary endocrine dyscrasias.

Apparently impotence may occur through gonad depletion or other mechanism, although it is difficult to distinguish from psychogenic impotence

The hypoglycemic fatigue syndrome in patients with brucellosis is being investigated. A flat glucose-tolerance curve with moderate hypoglycemia at the end of three hours (58 mg) was noted in 1 patient with chronic brucellosis of at least fifteen years duration Fatigue, depression, apathy, extreme weakness, sweating, tremulousness, and near-fainting occurred each late afternoon He had been ambitious and alert, in spite of his recurrent illness, until the past year since when he had lost all his former drive The symptoms were relieved by a sweet soda fountain drink and did not reappear after the evening meal. He was inordinately fond of sweets and starchy food One afternoon when he felt unusually well, with no fatigue, blood sugar was

found to be 95 mg. per cent. Alleviation followed a high protein diet containing no free sugar and between-meals feedings, as suggested by the work of Alexander and Portis.[8]

The exact implications of this syndrome when occurring in patients with chronic brucellosis are not clear. There may be an allergic or infectious basis for the hyperinsulinism but more likely it is psychogenic.

The working hypothesis advanced by Alexander and Portis was that certain emotional situations, characterized by loss of spontaneous zest and a revulsion against routine activities, caused a disturbance in the regulatory mechanism of the blood-sugar concentration. The emotional tension accompanying zest, enthusiasm, or interest keeps up a certain tonus; without emotional participation, the tuning up of the vegetative processes and the shifting of the sympathetic-parasympathetic balance in favor of increased sympathetic tonus does not take place, the organism then being engaged in continued activity without the corresponding metabolic adjustment necessary for sustained effort They considered that it is not the absolute lowering of the sugar concentration but the inability of the organism to raise the sugar concentration as it is needed during activity that causes the feeling of fatigue and exhaustion, and in some the tremulousness, light-headedness, and weakness.

Evidence of the influence of the vagus nerve on this mechanism was submitted Atropine, orally or by hypodermic, resulted in reestablishment of normal glucose-tolerance curves In some cases diet and atropine were most useful in breaking up the vicious circle, thus allowing a psychotherapeutic attack on the basic emotional problem In other cases the medical management was indispensable to insure the success of psychotherapy

LYMPHATIC SYSTEM

Lymphadenitis is of frequent occurrence in brucellosis, acute or chronic Anterior cervical, axillary, or inguinal nodes are most commonly affected, although at laparotomy or autopsy involvement of the retroperitoneal lymph nodes has been commonly observed. In one case simulating appendicitis inflammatory reaction in the lymph nodes in the region of the cecum was found

at laparotomy (p. 183). In various patients palpable tender swelling of very superficial lymph nodes was noted along with each recurrence of other manifestations of brucellosis. Infectious mononucleosis, or Hodgkin's disease, may be simulated

Simulation of or coexistence with Hodgkin's disease was first described by Parsons and Poston [526] in 1939.

The patient was a 26-year-old man Eleven months before his first admission to a hospital he began to have periodic attacks of fever ranging from 38 to 40° C, with general malaise, weakness, anorexia, chilly sensations, diarrhea, and slight cough, alternating with periods of good health There was generalized lymphadenopathy, with small, discrete, and tender nodes The spleen was palpable, soft, and slightly tender and there was tenderness in the region of the liver. Blood study was not remarkable except for a positive blood-agglutination reaction *in a dilution of 1:640 during the first admission, negative on all subse*quent admissions Phagocytic index for *Brucella* was "negative." Skin test with anti-*Brucella* goat serum was positive but the intradermal reaction to Brucellergen was negative He improved rapidly and was discharged after eleven days with a clinical impression of pyrexia due to Hodgkin's disease or brucellosis. Nine days after discharge he returned with a fever of 39 7° C Biopsy of a supraclavicular lymph node showed "chronic lymphadenitis with necrotic foci, suggestive of brucellosis, tularemia, or tuberculosis." There was nothing to suggest Hodgkin's disease histologically *Brucella* was grown from the node, and the organisms were agglutinated by known *Brucella* antiserum He was given anti-*Brucella* goat serum, receiving 60 cc. during the next seven days, and was discharged after thirty days of hospitalization He returned to the hospital four more times with essentially the same story and physical findings, each time having lost ground and in generally poorer condition Progressive anemia occurred and fever was higher and lasted longer He developed various abdominal and joint pains. During his third admission he was given *Brucella* vaccine, with no clinical or immunologic evidence of improvement Temperature usually subsided and he appeared better following blood transfusions After his fourth admission *Brucella* was isolated from bile A cholecystectomy was performed, with uneventful early postoperative reaction followed by fever from 39 to 40 6° C beginning on the eighth

day and lasting thirteen days He was given sulfanilamide with a rapid fall in his leukocyte count to less than 1,000 On his last admission he complained of pain in the left side of his chest, generalized pains, anorexia, and weakness. He was critically ill, emaciated, jaundiced, and extremely pale. He developed bronchial pneumonia and died (For report of the pathologic findings see page 133)

This patient did not have histologic evidence of Hodgkin's disease one year before death, but did have brucellosis At autopsy he still had brucellosis and lesions indistinguishable from Hodgkin's disease. In the 3 remaining cases which they reported, the first had injured a leg with ensuing lymphadenitis, diagnosed as Hodgkin's disease; the second developed a lesion in the mouth followed by cervical lymphadenitis, likewise diagnosed as Hodgkin's disease, the third case gave no history of trauma, having had gradual onset of enlarged lymph nodes in the right side of his neck From all of these patients biopsies of lymph nodes resulted in the recovery of *Brucella*. In all 4 cases, at the time that *Brucella* was recovered from lymph nodes, agglutination tests were negative. Observations of others are discussed on pages 132–138.

Isolation of *Brucella* from lymph nodes has been reported so frequently as to leave no doubt of the etiologic relationship between *Brucella* and some forms of lymphadenopathy In the presence of true Hodgkin's disease the isolation of *Brucella* from lymph nodes must be attributed to coincidence, in the absence of proof of etiologic relationship

FOCAL INFECTION

Alveolar abscess occurred in a large percentage of the cases reported in 1934 [298] and 1937 [299] Approximately 75 per cent of the 171 cases studied prior to 1937 revealed one or more abscessed teeth In one patient 28 abscessed teeth had been extracted. Subsequent observation revealed a smaller percentage of alveolar abscess, neglect of teeth in the population first studied was a

probable factor. Martinez[464] discussed the importance of dental infection in brucellosis No definite evidence has been produced that alveolar abscess is caused by the *Brucella* organism

Other focal infection has been discussed under regional symptomatology.

Chapter VI

DIAGNOSIS

The diagnosis is obviously difficult. It takes the use of everything at our command in the way of diagnostic procedure—agglutination reaction, skin tests, blood cultures, phagocytic index determination—but above all it takes a knowledge on the part of the doctor that this disease exists and must be considered in every case of protracted fever or other ailment of an infectious nature that he can't get to the bottom of (Kern)[898]

THE diagnosis of brucellosis, particularly in its chronic form, may be among the most difficult tasks in medicine. Clinical diagnosis rarely can be made with any degree of assurance. Usually no more than a suspicion of brucellosis may be entertained prior to laboratory study There are no pathognomonic signs in either the acute or the chronic stage. Brucellosis simulates so many other disease entities, often so exactly, that confusion with them, or of them with brucellosis, is at times inevitable

Physical findings usually are surprisingly few Therefore diagnosis must depend upon very careful history of past and present illness, symptoms, and signs, all of the multiple laboratory procedures, exclusion of other disease and history of possible exposure, sometimes supplemented by therapeutic test of treatment.

A positive history of exposure, through ingestion of raw milk or other dairy products, contact with live cultures or with infected animals, may strengthen the suspicion of brucellosis. A negative

history seldom can be stressed since almost everyone has had some form of exposure, even though unknown

Even with the use of the multiple tests that are available and with the most careful clinical consideration, diagnosis may be unsatisfactory.* Fully as important as the performance of the multiple tests and the manner in which they are performed is their interpretation. Each test has its own limitations which should neither be ignored nor overemphasized.

Insistence on positive blood culture as the sole criterion of diagnosis results in error in a large percentage of cases, particularly in the chronic phase.

Admitting that diagnosis by exclusion is not a sound clinical principle, Darley and Gordon [162] said that careful clinical evaluation of the *Brucella*-sensitive patient can, with reasonable accuracy, establish the presence of active infection. They felt that a diagnosis of brucellosis cannot be seriously regarded as probable until every other possible explanation for symptoms has been carefully considered and that the evidence appears to favor a low-grade type of chronic brucellosis ("indolent brucellosis") as a clinical entity The *Brucella*-sensitive patients' clinical evaluation is aided by the other laboratory procedures to be discussed.

The commonest errors in the diagnosis of brucellosis are. (1) to consider that negative blood-agglutination reactions, or reactions in low titer, rule out active *Brucella* infection, (2) to accept a positive intracutaneous reaction as the only laboratory evidence of active brucellosis, and (3) to perform the intradermal test prior to adequate previous laboratory study, resulting in the induction of agglutinins and opsonins by the skin-testing agent (pp. 341–343).

Aggregate Significance of Laboratory Procedures

Since it is the combined information from the multiple tests, rather than one test alone, on which the diagnosis of brucellosis usually rests, a brief consideration of the aggregate information

* Harris, H J Chronic brucellosis, the unsatisfactory status of current diagnostic methods *Am Jour Pub Health* 39 870, 1949

to be derived will be presented first, followed by discussion of the technic and significance of the individual tests.

There is general acceptance of the following concepts: (1) Positive cultural findings constitute the only incontrovertible proof of *Brucella* infection; (2) Blood-agglutination reaction in a titer of 1:80 or above is presumptive evidence of brucellosis; (3) Positive reaction to the intradermal test is evidence of past or present infection, signifying the degree of specific bacterial allergy of the patient to *Brucella;* (4) The opsonocytophagic reaction gives added significance to the other laboratory procedures and to clinical evaluation; (5) Negative reactions do not constitute evidence on which brucellosis may be ruled out.

Inclusion of the blood-complement-fixation reaction in the study of brucellosis may prove to be important, although many reports have tended to indicate its lack of significance. Perfection of an antigen may be the main stumbling block to its more general use, according to Schmidt.[603] Larson and Sedgwick[426, 427] presented data on the use of the complement-fixation reaction in the diagnosis of *Brucella* infection in children and infants. The reaction in the diagnosis of contagious abortion in cattle was described earlier.[425] Wise and Craig[716] stated that it has no advantages over the more easily performed agglutination test but that it may occasionally be useful in the diagnosis of acute brucellosis because complement-fixing antibodies frequently appear before agglutinins Menefee and Poston[475] considered it to have no advantage over the agglutination test Griggs,[280] however, found the test of some confirmatory value It is apparent that a complement-fixation reaction would have value if other laboratory study is negative or equivocal.

Borts[71] emphasized the difficulty, except under hospital conditions, of getting the cooperation of all concerned in the complete laboratory study of patients Blood culture was considered first in importance in making the diagnosis, followed by the agglutination, skin, and opsonic tests respectively That all tests other than culture—particularly the skin test—must be interpreted with cau-

tion, and that negative laboratory tests do not exclude the presence of the disease, was stressed.

Evans, Robinson, and Baumgartner[206] attempted to evaluate the four laboratory procedures from the study of 511 patients never previously studied with the aid of specific tests, with similar conclusions. Agglutinins in titers of 1:40 or higher occurred about 11 times as frequently, positive skin reaction more than 4 times as frequently, and a "positive" opsonocytophagic reaction about twice as frequently, in chronic brucellosis as in cases ill with other diseases

Leon and Sosa[435] skin-tested 298 supposedly normal persons and 78 persons known to have *Brucella* infections Of the group known to be infected, skin tests were positive in 89 per cent Among those considered normal, skin tests were positive in 16 per cent (47 persons) Of the 47 "normal" persons who gave positive skin reactions, 20 were further studied to detect active or past *Brucella* infections *Most of them gave a positive history, tending to bear out the author's view that the use of "normal" persons as controls in evaluating the various diagnostic procedures for brucellosis is of questionable significance Any or all may have or have had obscure* Brucella *infections resulting in varying degrees of skin, blood-agglutination, and phagocytic reactions*

Foshay[235] reported a unique approach to the question of the reliability of noncultural laboratory aids in diagnosis. Using the same test materials and adopting uniform methods of procedure and of interpretation of reactions, two groups of approximately 100 individuals each were tested, one by Calder in San Antonio, Texas, and the other by Foshay and his associates in Cincinnati, Ohio Skin tests with various antigens, agglutination tests with both *Brucella abortus* and *melitensis*, and phagocytic tests were performed. Calder's patients were largely those sent to him because of possible brucellosis, from cattle country and from areas close to goat-raising regions where pasteurization of milk was incomplete Foshay's subjects were patients selected at random largely from wards of a general hospital and a tuberculosis sanatorium, with some "normal" persons These persons were from

the region of Cincinnati where pasteurization of milk had been almost complete for twenty-five years and where cattle, goat, and hog raising was minimal. He expected to find a wide variation in the results in these two groups if the tests could be considered dependable, i.e., to find positive reactors in a high percentage of persons in parts of the country where brucellosis was known to be prevalent and a relatively low percentage in a region where the disease is seldom encountered, although searched for. A positive reactor was defined as one who gave clear-cut positive reactions to at least two of the tests Calder's group in San Antonio showed 91 per cent of reactors and Foshay's in Cincinnati showed 8 per cent. He felt that this was adequate evidence of the specificity of the tests.

Under "Current Comment" in the *J.A.M.A.*[375] the following succinct statement of the difficulties involved in the diagnosis of chronic brucellosis appeared.

> Brucellosis is one of the most important of the "new" diseases discovered in recent times by bacteriologic methods. As emphasized by Harris, brucellosis should receive consideration early in the diagnosis of obscure illness. Unfortunately there is as yet not available any easy adequate specific means of diagnosis of chronic brucellosis. The agglutination test is of significance only if positive. A positive intradermal test indicates increased sensitivity, but it does not tell whether the infection is still active Negative skin tests have been observed in active *Brucella* infection The opsonocytophagic test requires perfect technic with a virulent *Brucella* strain. Increased phagocytosis with a positive skin test, the symptoms suggesting brucellosis, points to a still active infection. The only definitely diagnostic procedure is isolation of *Brucella* by culture from the patient. This concerns one of the "most difficult of all bacteria to isolate!" and the cultural methods now in use are hardly practicable for daily routine work in the clinical laboratory . A better understanding of various chronic infections certainly requires more adequate cultural study, with special reference to the detection of brucellosis The importance of this infection calls for the organization of cooperative investigations of the problems of diagnosis and treatment

Simpson[630] issued the following caution:

The value of the agglutination test and the skin test has been adequately demonstrated, but it must be recognized that all of the so-called specific diagnostic tests may yield repeatedly negative results in culturally proved cases of brucellosis, and that none distinguishes with certainty between present and past infection Thus in the absence of bacteriologic proof, the findings of positive agglutination tests, skin tests and opsonocytophagic tests must be weighed carefully in the balance of fine critical observations before a decision is reached Just as the diagnosis of brucellosis may be missed by too great reliance on any one or all of the diagnostic tests, so also is there danger that the diagnosis may be made much too freely by unjustified reliance on a positive skin test. This hazard pertains particularly to the diagnosis of chronic brucellosis

The multiplicity of the tests for brucellosis and the equivocal significance of each individual test, except culture, may be a source of confusion. Their very existence may be looked upon as evidence of their inadequacy. However, their aggregate value is greater than that of the available laboratory procedures for many other conditions.

Individual Diagnostic Procedures

BLOOD-AGGLUTINATION REACTION

Next to culture of the organisms, the blood-agglutination reaction is the most reliable available evidence of active infection, when positive *Absence of agglutinins is without significance* Carpenter, Boak, and Chapman[122] stated that agglutinins are not passively absorbed through the gastrointestinal tract, but are actively produced following invasion of the tissues by the organism. Hardy and his coworkers[297] considered that *Brucella* may establish itself in some focus in the body and stimulate antibody production apart from any manifestations of the disease. Under such circumstances the patient is potentially ill with brucellosis since exacerbation may occur at any time (pp. 67, 284)

There is still controversy concerning the significance of negative blood-agglutination reactions. Debono[161] stated that a negative blood-agglutination reaction in the presence of a positive blood culture is exceedingly rare and that it is dangerous to diagnose brucellosis in the face of a persistently negative serum reaction. This divergence from the opinion of almost all other workers may be explained by the fact that *Brucella* agglutinins are found more often in *melitensis* infection than in the *abortus* type. Debono's observations are applicable to acute infections, particularly with the goat variety.

No acceptable evidence has been submitted as to the value of negative blood-agglutination reactions in ruling out brucellosis Shaughnessy and Grubb[623] considered that negative blood-agglutination reactions were accurate in 90 per cent, basing their conclusions on answers to questionnaires sent to physicians who had submitted 358 specimens of blood giving negative agglutination tests In at least 86 per cent of the cases the negative agglutination test substantiated the physicians' diagnoses. It was not stated in what manner, other than by the negative blood-agglutination reaction, brucellosis in clinical or subclinical form was ruled out

In the chronic phase of brucellosis the finding of a positive blood-agglutination reaction in a significant titer is the exception rather than the rule Brucella *has been cultured by many workers from patients with negative blood-agglutination reactions.*

Amoss[16] reported an instance of intermittent hydrarthrosis of seven months duration with positive blood culture and recovery of the organism from joint fluid but with persistently negative blood-agglutination reactions with homologous and other strains of *Brucella*

Baker[34] also reported intermittent hydrarthrosis, with positive culture of blood, synovial fluid, and urine, in the presence of negative blood-agglutination reaction

Agglutinins are likely to be fleeting in any stage of the disease and to bear no constant relationship to activity of the infection, especially when localized Amoss noted no relation between recovery from infection and the agglutination titer He quoted a

second case of local infection with *Brucella* which gave rise to incapacitating symptoms without agglutinins in the blood, *Brucella* was isolated from bile on duodenal drainage, from bile and gallbladder at laparotomy, and from a hemorrhagic ovarian cyst. Agglutinins had been present seven years before and *Brucella* had been isolated from the blood

Agglutination titers were found useful for diagnosis but not for prognosis in a series of 17 cases of laboratory infections reported by Howe and his coworkers [345] The height of the titers was not proportionate to the severity of the illness, nor did it show consistent variations with remissions or exacerbations.

In a case of *Brucella suis* meningitis [513] with positive spinal-fluid culture, agglutinins were present early in the course of the illness in a dilution of 1.80 but disappeared within a few weeks following improvement and did not reappear during the protracted course of recovery.

Poston [537] reported positive cultures in 5 of 14 patients with chronic illness suggesting brucellosis in whom blood-agglutination reaction was negative in 2, present only in a very low dilution in 1, and in a titer of 1·40 in 2

Many others also have reported negative blood-agglutination reactions, or agglutinins in low titer only, in the presence of positive culture of blood or from localized infections,[99, 122, 201, 258, 362, 365, 366, 455, 540, 641, 660] in acute and chronic illnesses

In an epidemic of *Brucella melitensis* infection, Huddleson and Munger [363] found 3 cases of clinical illness with positive blood cultures but with no blood agglutinins Blood cultures were positive in 12 other clinical cases which showed a maximum agglutination titer of 1.25 at the time

Bevan [57] stated that "apparently agglutinins are not synonymous with immunity although an indication of it." In the earlier cases reported by the author [299, 299, 302] it was so often noted that the agglutination titer rose in response to *Brucella abortus* vaccine, coincidentally with clinical recovery, that the impression was attained that there was an important correlation between agglutinins and immunity. Later it became evident that there was

no definite correlation. *It is also an erroneous concept that lessening of the agglutination titer is of favorable prognostic import.*

Effect of Fever on Agglutinins

That fever due to any cause may increase agglutinins against *Brucella*, "whether the person has or has not had a clinical infection with undulant fever in the past," was considered probable by Dooley.[180] Of 11 boys found to have positive agglutination reactions in low titers (1:10 to 1:40), 7 developed a rapid increase in agglutinins during the course of other subsequent febrile illnesses. In 1 instance the increase was from 1:80 to 1:640 in one week. These boys had had "subclinical" infection with *Brucella* during the course of an outbreak in a boys' school It is possible that blood-agglutination titers might have risen had they not had intercurrent febrile illnesses. Relapse of brucellosis in the course of the intercurrent febrile illness also must be considered Under any circumstances, blood-agglutination reactions following *Brucella* infection are unpredictable.

Menefee and Poston[475] *revived this theory, based on observations* on 9 students who became ill with streptococcic sore throats while under study to determine the significance of standard laboratory procedures used in the diagnosis of brucellosis A well-defined increase in agglutination titers and also in the phagocytic power of the white cells was observed during the course of the intercurrent illness However, analysis of their observations reveal that there was a commensurate rise in agglutinins and opsonins in the 20 other persons not ill with streptococcic sore throats. The 9 who developed septic sore throats and the 20 who were not ill all had had skin tests with Brucellergen three weeks before Apparently the tendency of agglutinins and opsonins to rise in response to intradermal tests with any *Brucella* antigen was not considered

Agglutinins in Apparently Well Persons

Agglutinins found in apparently well persons usually are considered of little or no significance, especially in those whose occu-

pations involve exposure to contact infection. It is more accurate to consider these persons as potentially ill, based on observations that many of them develop clinical evidence of active disease at some future time. Illustrative is the patient mentioned by Hardy and his coworkers [295] During an epidemiologic survey of packing-house employees in October, 1928, a 21-year-old man was encountered who felt well although his serum agglutinated *Brucella abortus* in a 1 2560 dilution. One month later he complained of profound weakness and stopped work. An acute attack of brucellosis ensued and *Brucella suis* was isolated from his blood. He died of myocardial failure.

Other experiences, published and unpublished, attest the fact that agglutinins against *Brucella* usually are significant when present Three children, apparently well, aside from an apparent anemia and a little lassitude, were reported by Borts [71] to have blood agglutinins in high titer in the course of an epidemic of milk-borne *Brucella suis* infection. They did not miss a day of school They might have been called well if one were to ignore the possible importance of agglutinins in apparently well persons [180, 475, 623] However, *Brucella suis* was isolated from their blood Agglutinins may not be ignored unless their presence can be explained. The patient may have to be kept under observation for prolonged periods to clarify his status

Cross Agglutination

Cross agglutination occurring in the presence of infection with *Pasteurella tularensis*, *Salmonella typhosa*, and *Bacillus flexneri* (and perhaps in certain rickettsial and viral infections), usually in low titer, seldom needs to cause confusion in the light of clinical and other laboratory evidence Such agglutinins are likely to be present in low titer, whereas agglutinins against the infecting

his coworkers [190] confirmed these observations, finding titers as

high as 1:500 in persons inoculated with cholera vaccine. Their studies suggested that there is an H antigen in *Vibrio cholerae,* which is also present in *Brucella.*

These so-called cross agglutinations may be anamnestic or memory reactions, occurring in patients who have had *Brucella* infections in the past. Borts [71] pointed out that in clinical typhoid fever, *Brucella* agglutinins may appear early but rarely go beyond 1:80 or 1:160, whereas the typhoid agglutinins developed in progressively higher titers, as high as 1:640 or 1:1280. The *Brucella* agglutinins recede promptly.

Shaughnessy and Grubb [623] found positive blood-agglutination reactions with *Brucella* antigens, some in high titer, in 4 and 9 per cent of blood specimens from patients in two tuberculosis sanatoria. The fact that the agglutinins were fleeting in a majority of these patients (25 and 9 cases respectively), disappearing within a week, and that none of a group of 8 controls gave positive skin reactions with "Brucin," helped to confirm their feeling that they were dealing with a nonspecific agglutination phenomenon rather than *Brucella* infection. Coexistence of *Brucella* infection and tuberculosis or anamnestic reactions in patients previously ill with brucellosis may have explained these findings.

Effect on Agglutinins of Intradermal Antigens

The intradermal test should be deferred until all information obtainable from the agglutination reaction has been secured. Otherwise, agglutinins may be stimulated, as may opsonins. This is particularly important in the acute febrile illness, where an agglutination response usually will occur, ultimately. In 1 patient [310] with prolonged, severe illness and extreme hyperpyrexia the diagnosis of brucellosis necessarily rested on blood-agglutination reaction, history, and exclusion of other disease. Cultures had been consistently negative. Blood-agglutination reactions, previously negative, became positive in high titer (1:320 to 1:640) eighteen months after the onset of the relapsing illness. *Had a cutaneous test been performed at any time prior to the blood-agglutination reaction,* agglutinins might properly have been at-

tributed to the skin-testing antigen, resulting in absolute confusion. (See page 157.)

In the chronic illness, where there is little expectation of finding agglutinins, skin test need be withheld only long enough to allow performance of blood-agglutination reaction and opsonocytophagic test, on one or more occasions.

The effect of intradermal tests on the production of agglutinins is discussed in detail on pages 341–343

Agglutinin-"Blocking" Property in Brucellosis Serums

Failure of agglutinins to appear or their tendency to disappear after once being present in cases wherein the disease process continues was noted by Griffitts.[277] He considered the absence of agglutinins in apparently active disease not to have been well explained. He found that serums freshly drawn from individuals known to have been infected with *Brucella* had the property of "blocking" the agglutination of *Brucella* organisms in a saline medium, that these serums agglutinate *Brucella* organisms when

and that serums from certain of these individuals agglutinate heavy suspensions (10 to 20 per cent by volume) of *Brucella* organisms suspended in serum or albumin solution on a warmed glass plate, although agglutinins were not found in test tubes with saline.

Agglutination Reaction in Synovial and Other Fluids

Agglutination reactions may be of importance when performed with synovial, pericardial, pleuritic, ascitic, hydrocele, spinal, or other fluids. In the absence of positive culture or blood-agglutination reaction in high titer such agglutinins may lend some support to a tentative diagnosis of brucellosis or to attract attention to the possibility of such an infection

Microscopic and Macroscopic Methods

The macroscopic tube blood-agglutination reaction is almost universally employed The microscopic agglutination test may be

employed as a qualitative test, preliminary to the macroscopic method. Lehr[412] stated that the microscopic method is quantitatively inaccurate, having an uncertain endpoint, but that it is useful because of its rapidity and the requirement of little blood and a minimum of apparatus. If the microscopic reaction is positive, the macroscopic tube test is performed to determine the exact titer. He considered the microscopic method better than the macroscopic in confirming the clinical findings in long-standing *Brucella* infections in which the agglutination titer cannot be expected to be high. Both methods are employed routinely in the author's work to serve as a check on each other. The macroscopic rapid-slide method has seemed to be the least accurate.

The microscopic blood-agglutination reaction may be of confirmatory value in the presence of other equivocal clinical and laboratory evidence of *Brucella* infection, especially when the macroscopic blood-agglutination reaction is negative, and the microscopic reaction partial, as sometimes occurs. For example, a 35-year-old man with nummular keratitis (p. 252) had been in close contact with goats, had drunk their raw milk, and had dressed fresh animal pelts and hair from fresh carcasses. Microscopic blood-agglutination reaction was partial in a titer of 1:80, macroscopic (tube) agglutination reaction was negative. The opsonocytophagic reaction showed marked phagocytosis in 1 cell, moderate in 3, slight in 16, and none in 5, a numerical index of 29 (often referred to as a "positive" phagocytic index) Skin test was positive The partial microscopic agglutination reaction, along with the suggestive phagocytic index, positive skin test, and clinical evidence of brucellosis had sufficient confirmatory value to justify a trial of *Brucella* vaccine therapy, with excellent response.

Blood-agglutination reactions were performed in the author's laboratory, using Brucella abortus organisms, strain No. 322, and the macroscopic agglutination reaction was determined on part of the same blood specimen by the Division of Laboratories and*

* This, and other work, was aided by a grant from the Committee on Scientific Research of the American Medical Association

Research of the New York State Department of Health, using the same strain of *Brucella,* on 70 blood specimens from patients referred because chronic brucellosis was suspected. The microscopic agglutination tests were carried out in dilutions of 1:40 and 1:80 only, as screening tests. (The test may be carried through successive higher dilutions if desired.)

The following results were obtained:

In 47 sera both microscopic and macroscopic agglutination reactions were negative (no discrepancy in 67.1 per cent).

In 6 sera there was slight to partial microscopic agglutination in the presence of negative macroscopic agglutination reactions (minor discrepancy in 8.0 per cent).

In 7 sera there was negative microscopic agglutination in the presence *of positive macroscopic agglutination in titers of 1:10* or 1:20 (minor discrepancy in 10.0 per cent).

In 5 sera there was partial microscopic agglutination in 1:40, or 1:40 and 1:80 dilutions, in the presence of a trace of agglutination in low titer only in the macroscopic reaction (essential agreement).

In 4 sera there was complete microscopic agglutination in titers of 1:40 in the presence of complete agglutination in the macroscopic reaction in titers of 1:10 or 1:20 (minor discrepancy in 5.0 per cent).

In 1 serum there was complete microscopic agglutination in titers of 1:40 and 1:80 in the presence of macroscopic reaction in a titer of 1:640 (no discrepancy shown since microscopic agglutination reactions were not carried beyond dilutions of 1:80).

It is therefore apparent that when complete microscopic agglutination occurs, macroscopic agglutination reaction may be expected to correspond, although not necessarily in exactly the same titer, tending to confirm Lehr's observations.

Microscopic Agglutination Reaction

The microscopic blood-agglutination reaction may be performed as follows.

Approximately 10 cc. of blood are collected by means of a dry sterile syringe or by blood-letting needle and allowed to clot in a sterile test

tube at room temperature. When sufficient blood serum is separated from the clot 0 05 cc. of serum is pipetted into a small test tube containing 1.0 cc. of sterile normal saline, giving a serum dilution of 1:20 A loop of this serum-saline mixture plus a loop of a fresh 48-hour culture of a smooth strain of *Brucella abortus* are mixed together on a cover glass and inverted over a hanging-drop slide, thus giving a 1:40 dilution.

To prepare a 1:80 dilution, 0.05 cc. of blood serum is placed in a small test tube containing 2.0 cc. of sterile normal saline, giving a serum dilution of 1 40; one loop of this serum-saline mixture is added to one loop of a culture of a similar density on a cover glass and inverted over a hanging-drop slide

As a control, one loop of culture is added to one loop of saline on a cover glass. The three slides are incubated for one hour at 37° C and then read.

Further dilutions may be used if it is desired to use this method as more than a screening technic

The microscopic technic may be essential when only a small amount of serum is available.

Macroscopic (Rapid-Slide) Agglutination Reaction

The macroscopic slide agglutination test may be performed as follows.

A glass plate ruled with one-inch squares or a glass slide with multiple wells designed for the purpose may be used The patient's serum is distributed in each square or well in 0.16, 0 08, 0 04, 0 02, 0 01, 0 005, and 0 002 cc. amounts. The antigen should be shaken vigorously before using When a drop of antigen (which may be obtained commercially *) is added to each quantity of serum, dilutions of 1·10, 1.20, 1.40, 1.80, 1.160, 1.320, and 1.640 are obtained If dilutions beyond 1 640 are to be used, the patient's serum should be diluted with physiologic saline for ease of measuring Antigen controls made with known positive and negative sera, should be made daily.

Serum and antigen are mixed with a toothpick or small glass rod,

* Pitman-Moore's *Brucella* antigen or Lederle's Febrile Antigen (*Brucella Abortus*).

progressing from the greatest dilution (i.e., from the smallest to the largest amount of serum). The mixture should be warmed, approximately to body temperature. The glass slide is gently rotated while the drops are watched for clumping over a period of three minutes. (After a longer time nonspecific clumping may occur because of drying.) Agglutination (flocculation or clumping) is readily seen with the naked eye, usually more easily against a black background.

The degree of agglutination may be expressed as complete (4+) when there are small areas of clear fluid between the clumped antigen, partial (3+), with partial clumping and slight cloudiness of the remaining fluid, slight (2+), with little clumping and virtually no clearing of the fluid, faint (+), with barely perceptible change, and negative (−), with no change in the mixture of serum and antigen. If in doubt as to the occurrence or completeness of agglutination in the slide technic, it may be viewed microscopically.

Nonspecific reactions may occur under circumstances discussed elsewhere (p. 285). The test has the same general value and limitations as the tube-agglutination method. It is thought by some to give results almost exactly comparable to the tube method and by others to be only roughly comparable. Although an insufficient number of comparisons have been made in the author's laboratory on which to base conclusions, a few marked discrepancies have been noted in that agglutination occurred in high titer in the rapid-slide method, with none or in low titer only in the macroscopic tube method and in the microscopic method. It is not recommended as the sole technic.

Huddleson[346, 351] described a rapid-slide agglutination technic applicable to blood serum, milk serum, and whole blood.

Macroscopic Tube Agglutination Reaction

For the macroscopic tube agglutination reaction 10 cc. of blood is placed in a sterile test tube and allowed to clot.

The method used by the Division of Laboratories and Research of the New York State Department of Health[683] is as follows:

Serum is separated from blood clot or blood cells by centrifugation for five minutes at approximately 1000 r.p.m., either in the original specimen tube or in a centrifuge tube. The clear serum is removed with a capillary pipette and 0.6 cc. of a 1:5 dilution of the serum-

saline mixture is inactivated by heating at 55–65° C. for thirty minutes. Dilutions of 1:10, 1:20, 1:40, 1:80, 1:160, and 1:320 are made. (Higher dilutions of 1:640, 1:1280, 1:2500, 1:5000, 1:10,000, or even 1:20,000 may be necessary to establish the exact titer and to avoid the prozone reaction referred to on page 293.) The serum dilutions prepared are combined with alcohol-treated suspension of *Brucella abortus*, incubated at 48–52° C. for four hours, refrigerated overnight, and the reaction recorded.

Centrifugation for ten minutes at approximately 2000 r.p.m. often demonstrates agglutination when it was not apparent before. If definite agglutination occurs in a 1:20 dilution or greater only after centrifuging, the test is repeated and another specimen obtained. Otherwise, the greatest dilution in which definite agglutination (4+ or 3+) occurs before centrifuging is reported.

If the blood is hemolyzed or the serum cloudy, a stained preparation is made to determine the presence of contaminating microorganisms. If no bacteria are found or if those present resemble pathogenic species, the clot is cultured. Contaminating microorganisms or exposure to extreme heat or cold, which also produces hemolysis, may affect the agglutination properties. The results of examination of specimens that are apparently chylous, those to which an anticoagulant has been added, and those received five days or more after collection are considered questionable.

Whole blood is preferred for serologic tests because contamination or hemolysis in serum alone is less readily detected. An equal volume of glycerol C.P. acts as an efficient preservative for serum for the agglutination test alone but renders the specimen unsatisfactory for complement-fixation tests.

For method of preparation of alcohol-treated suspensions of *Brucella abortus* for use in the agglutination test and for other details the reader is referred to Wadsworth.[959]

Huddleson[348] described the technic for the macroscopic tube-agglutination reaction as adopted by the United States Livestock Sanitary Association, which he considered as equally applicable to human or cattle blood serum. He expressed the opinion that there was no advantage in the use of separate or combined antigens made of each species, stating that an antigen made of an

S strain of *Brucella abortus* is satisfactory for detecting the agglutinins produced by all three species of *Brucella*. There is some controversy on this point. Shaughnessy and Grubb[623] agreed with Higginbotham and Heathman that a polyvalent antigen, including some local strains, should be employed. Angle, Algie, and Morgan[24] pointed out the wide variation in agglutination titers reported by various laboratories, stating that in many cases the difference in results were too great to be caused by technical variations For example, a state laboratory reported a negative *Brucella* agglutination reaction on the same serum in which they were able to demonstrate a positive titer of 1:640 with three commercial antigens. The necessity for standardization of *Brucella* polyvalent antigen for agglutination tests was pointed out. Griggs[279] expressed agreement with these observations Whether the fault lies in the valency of the antigen or the smoothness of the strain or other factors is not clear The Division of Laboratories and Research of the New York State Department of Health[255] employs but a single smooth strain of *Brucella abortus*. This has seemed satisfactory in the author's work, using the microscopic technic.

Evans[203] tested one lot of serums against two *Brucella* antigens, prepared with variety *abortus* No. 456 and variety *melitensis* No 428, respectively *In the majority of positive samples the agglutinin reactions with the* melitensis *and* abortus *antigens were in the same dilution or differed by only one step in the series* In the case of 16 serums (1.6 per cent) there was a more marked difference in the titers as determined by the two antigens For example, one serum reacted with the *abortus* antigen in the 1:80 dilution but failed to react with the *melitensis* antigen Another serum reacted with the *melitensis* antigen in the 1·40 dilution but failed to react with the *abortus* antigen.

Zone Phenomenon

A zone phenomenon, also referred to as a "prozone reaction" and as a "pre-agglutinoid zone" may occur Hardy and his coworkers[293] noted that in dilutions of 1 80 or even 1:160 no agglutination may occur, while in higher dilutions clear-cut reactions

may occur, pointing out that sera must be examined in high as well as in low dilutions. Amoss [10] referred to one case in which there was no agglutination until a dilution greater than 1:1,200 was reached, although there was complete agglutination from that point to 1:20,000. Carpenter [113] pointed out that dilutions of serum should cover sufficient range, preferably from 1:10 to 1:1,280, because of the prozone reaction which occasionally occurs, showing no agglutination at 1:10, 1:20, or 1:40, but agglutination in dilutions of 1:80 and higher.

CULTURE

Culture of *Brucella* from the blood, bile, feces, or urine or from spinal, synovial, pericardial, ascitic, pleuritic, or other fluid or from biopsy or operative specimens, discharge, secretion, exudate, or transudate from localized infection, is the most conclusive evidence of the existence of the disease. If routine cultural methods are used, rather than the special methods for the isolation of [illegible]
[illegible]
to be recoverable with relative ease. *Brucella suis* usually is less readily recoverable. *Brucella abortus*, particularly in the chronic phase, may be exceedingly difficult to isolate.

Spink and Hall [143] over a period of seven years attempted culture repeatedly in more than 100 patients whom they strongly suspected of having brucellosis. The organism was isolated from only 10 individuals (all of the *abortus* variety). Among the patients 35 had been considered as having an active form of the disease. Thus it is seen that bacteriemia was demonstrated in less than one-third of those in whom it might reasonably have been considered to exist These results emphasized the difficulties in obtaining positive cultures, especially in *Brucella abortus* infections

Simpson [630] stated "When clinical suspicion is aroused recourse should be had to the several confirmatory tests Since the diagnosis can be established with absolute certainty only by recovery

of *Brucella*, repeated attempts should be made to culture the organism from the blood, urine, bile, spinal fluid, exudates and excised tissues. Hospitalization is desirable because such bacteriologic studies can be carried out more efficiently in a well-equipped hospital." Unfortunately, few hospital laboratories are prepared to carry out the cultural procedures essential for the isolation of *Brucella*. The erroneous conclusion that brucellosis has been ruled out because of negative cultural study may result, even though inadequate methods have been used.

Borts[71] noted that in the taking of blood cultures twice daily it was not unusual to find a culture taken at 9:00 A.M., when the temperature was near normal, to be negative whereas *Brucella* were isolated when the culture was taken in the latter part of the same day, at the height of the fever. Spink and Hall[643] obtained blood for culture every other day for at least three times in acute cases and less frequently in chronic cases.

In a group of 17 patients suffering from laboratory infections[345] cultures were occasionally positive during periods when symptoms were minimal and when temperatures were normal throughout the day. The relative ease with which the organisms were recovered in 15 of the 17 patients is probably ascribable to the strains involved (*suis* and *melitensis*) and the fact that the patients were infected with laboratory strains.

The success of culture may depend on pure chance, the organism may be circulating in the blood at unpredictable intervals (p. 296).

Although recovery of *Brucella* may be successful in only a small percentage of patients, particularly in those not acutely ill, the value of the procedure when successful is so great as to justify many repeated attempts (p. 296). Not infrequently cultural findings are positive in the absence of any other laboratory evidence of brucellosis. Poston[537] reported isolation of *Brucella* from 5 out of 14 patients with obscure chronic disease, using the technic described on page 303. Robinson and Evans,[580] in discussing these patients, stated that in none of the 5 cases was the agglutination

titer as high as 1:80. In 2 cases the agglutination reaction was negative; in 2 others it was positive in a titer of 1:40, and in the 5th case agglutinins were demonstrated only in low dilutions. All 5 patients had been ill for more than six months when the agglutination tests were performed. Only 1 of the 5 patients gave a definitely positive intradermal reaction. One patient gave repeated "negative" opsonocytophagic reactions, the other 4 patients showing opsonocytophagic reactions varying from weak to strong. There was no opportunity to repeat the blood cultural studies in the patients giving negative results. *Brucella suis* was isolated in 1 patient, *melitensis* in 3, and *abortus* in 1.

The significance of positive blood cultures was brought into question by the recovery of *Brucella melitensis* from the blood of 3 symptom-free persons, among 49 subclinical infections reported by Huddleson and Munger.[365] No symptoms of brucellosis were noted before or after the cultures were obtained. They concluded that "one may be infected with *Brucella* and never show clinical symptoms of the disease." Obviously it may not be safely inferred that these persons will remain well (pp. 67, 284).

Isolation of *Brucella suis* from the blood of 1 of the author's patients was accomplished within five days although the patient was not acutely ill, with fever of 100° F (p 441). In another chronic illness *Brucella* was isolated from uterine discharge following a third spontaneous abortion (p 195). In a third patient *Brucella melitensis* was isolated on the sixth attempt, four years after symptoms began, following remission of a subacute exacerbation. In 2 other patients (one subacutely and the other chronically ill) *Brucella abortus* was isolated from the blood in the author's laboratory although no organism was recovered from their blood in three institutional laboratories.

Many factors may combine to prevent recovery of the organism, among them poor technic, inherent technical difficulties, and indifference.

Prolonged Incubation, Frequent Subculture, and Animal Inoculation

Prolonged incubation of cultural material, frequent subcultures, and animal inoculation all may be essential to success. The isolation of *Brucella* may be possible only through animal inoculation.[113, 537, 539, 580]

Hardy and his coworkers[295] considered prolonged incubation to be of first importance, pointing out that growth occasionally may be evident on the fourth day if a subculture is made but that it may be the third or fourth week before the organisms have multiplied sufficiently to be evident if subcultures are not made, particularly if the *abortus* strain is involved. They incubated broth cultures for four weeks with subcultures at semiweekly intervals before reporting no growth. These methods are costly and time-consuming, requiring as long as four and a half months in some instances, but are strongly recommended. Attempts are being made to improve cultural methods so as to render animal inoculation less essential.

Isolation of Brucella *from bone marrow* in 93 per cent of 45 cases of brucellosis as compared with 20 per cent in recovery of the organism from the blood, was reported by Cattaneo[134] He found that bone-marrow culture was also positive in a small percentage of brucellosis patients discharged as clinically recovered, and proposed this procedure as an indispensable check in such cases to avoid late recurrences The strain involved in all these cases was *Brucella melitensis*. He cited the similar results reported by Signorelli, Baserga, and Barbagallo. Further investigation is necessary. It is unlikely that the *abortus* strain can be recovered from bone marrow so readily, particularly in the chronic phase. Rosenthal[597] is of the opinion that no information is to be gained by culture of bone marrow that cannot be obtained by culture of blood However, Spink[642] reported isolation of *Brucella abortus* from the sternal marrow and blood of one patient with chronic brucellosis and from sternal marrow but not from venous blood in another This experience serves to reestablish the value of this

simple procedure, particularly since material is thereby made available for histologic study. The typical granulomatous lesions of *Brucella* infection may be demonstrated, as was done by Spink in 4 chronic cases.

Material for culture should be very fresh, reaching the laboratory immediately after collection, preferably within an hour, so that inoculation into suitable media may be undertaken at once. (In a unique instance *Brucella* was isolated from uterine discharge in glycerol, mailed to a laboratory 135 miles away [p. 195].) Whenever possible it is preferable that the material for culture be collected at the laboratory where the cultural study is to be undertaken.

Negative cultural findings have no significance.

Various methods of culture, adaptable to the material to be studied, have been described. Many, not found in standard texts on bacteriology, are included here because of some special virtues in each. The varying growth requirements of the various strains of each species suggest that no single technic is applicable to all.

Culture Media

Discussion of preparation of culture media will be limited to those needed in the small laboratory interested especially in isolation of *Brucella*. Media and methods of preparation for general bacteriologic examination may be found in standard texts on bacteriology and laboratory methods.*

Attempts to improve the media for the isolation of *Brucella* have been made by many [206, 364, 398, 411, 421, 469] Commercially available tryptose agar and broth (Difco) may be considered standard for the small laboratory, allowing isolation, propagation, and differentiation of *Brucella* of the three species. If the presence of pathogenic or contaminating Gram-positive bacteria is suspected, crystal violet may be added to produce a final dilution of 1:1,000,000, to inhibit their growth without interfering with the growth of *Brucella*.

* Such as Wadsworth's *Standard Methods of the Division of Laboratories and Research of the New York State Department of Health* (Ed 3) Baltimore, Williams and Wilkins, 1947

Bacto-Tryptose Agar
Tryptose Agar (Dehydrated)—Difco

Composition (per liter)

Bacto-tryptose	20 Gm.
Bacto-dextrose	1
Sodium chloride	5
Bacto-agar	15

Suspend 41 Gm in 1000 cc of cold water and heat to boiling to dissolve the medium completely Sterilize in autoclave at 15-lb pressure (250° F., 121° C) for 20 minutes

Bacto-Tryptose Broth
Bacto-Tryptose Broth (Dehydrated)—Difco

Composition:

Bacto-tryptose	20 Gm
Sodium chloride	5

Dissolve 25 Gm in 1000 cc. of distilled water and sterilize in autoclave for 20 minutes at 15-lb. pressure (250° F., 121° C.) The final reaction will be *p*H 6 9 ±. It should be freshly prepared If not used the same day as sterilized, heat in boiling water or flowing steam to remove absorbed oxygen and cool quickly, without agitation, just prior to inoculation

Bacto-Tryptose Agar with Crystal Violet

Where Gram-positive contaminants are present, as in infected milk, crystal violet (gentian violet) is used in a final concentration of 1:700,000 in tryptose agar To secure the proper concentration 1.4 cc. of 0 1 per cent solution of bacto-crystal violet (DC-3) is added to each liter of tryptose agar before sterilization

Beef or liver infusion agar and broth may be used Huddleson[371] stated that this peptone-broth medium (bacto-tryptose, Difco) will yield as much growth in forty-eight hours as liver broth will yield in ten days, if liver infusion from one-fourth pound of liver is added to a liter of bacto-tryptose broth, growth will continue for many weeks

For propagation of *Brucella* for performance of the opsonocytophagic test or preparation of antigens for the blood-agglutination reaction, bacto-tryptose agar has proved a more satisfactory medium than liver infusion agar. Laboratory strains of *Brucella*, having become adapted to growth in the absence of extra CO_2, grow well on this medium which would be unlikely to support growth of the naturally occurring species requiring extra CO_2. Transfers are made daily in preparation of forty-eight-hour growths for performance of the opsonocytophagic test.

For differentiation of *Brucella* species bacto-tryptose agar with thionin and basic fuchsin are satisfactory. However, since certain differentiation may require more than this dye-differentiation method, complete laboratory facilities are usually needed. Methods of differentiation are discussed on pages 27–33.

For submission of specimens of blood or other uncontaminated fluid or tissue to laboratories, bacto-tryptose broth autoclaved in rubber-capped flasks is satisfactory

Danger to Laboratory Personnel

Because of the highly infectious nature of the microorganism, rigid precautions are advocated. Gilbert[256] made the following recommendations.

Insofar as is practical, working with an assistant in a room fully equipped and assigned for the purpose is advised Special gowns and, when necessary, rubber gloves, goggles and masks, should be used and placed in a container in the room for sterilization after use At the end of the work day, the working space and nearby floor is washed with 1 per cent cresol. Needles and loops should be heated with particular care after use, to avoid spattering Use of a safety pipette filler or mouthpiece and opening and closing of all containers by an assistant is recommended Other precautions advised are to hold the tip of the pipette over a Petri plate containing cotton saturated with 1 per cent cresol to catch any drops that may fall, to store cultures and specimens in locked cupboards or in containers bearing the name of the *microorganism and the warning "caution" in red pencil,* to discard contaminated apparatus in metal containers and to place them in a

sterilizer, and to mark containers "Do Not Touch" if there is not space for them in a sterilizer.

Employment of personnel well trained in bacteriologic technic is essential. Additional data on laboratory infections due to *Brucella* and precautions that should be observed appear in the chapters on epidemiology and prophylaxis.

The fear of *Brucella* infection of laboratory origin has led many hospitals and other laboratories to refuse to carry out necessary procedures involving these organisms. This overcautiousness has contributed to the backwardness of many institutions in the diagnosis of brucellosis.

Blood

Cultural technic and methods for animal inoculation employed by the Division of Laboratories and Research, New York State Department of Health,[649] are as follows: *

Inoculate semisolid agar and blood agar plates as directed below. Incubate † cultures on solid media in the presence of 5 to 10 per cent CO_2. If growth is not observed at the end of a week, transfer 0.5 cc. and 3 cc. amounts of each semisolid-agar culture to a blood-agar slant and a bottle containing 50 cc of semisolid-agar medium, respectively. Reexamine at weekly intervals for at least six weeks unless a member of the genus *Brucella* or some other significant species is isolated or the presence of contaminating microorganisms renders further examination impracticable.

When small, nonmotile, Gram-negative bacilli morphologically typical of *Brucella* are isolated, test for agglutination in specific dilutions of known serum

If the blood for culture was collected following the administration of a sulfonamide or penicillin, use a semisolid medium to which has been added *p*-aminobenzoic acid or its sodium salt, or a penicillin inactivator, respectively.

When clot of blood is to be examined, remove the serum for serologic testing using a capillary pipette fitted with a small rubber bulb.

* For a full discussion of all phases of laboratory methods see Wadsworth, *op cit*

† Incubator temperature should not exceed 37° C The desirable range is from 35 to 37° C

Follow the technic recommended by Sellers for comminuting the clot: Place the barrel of a 10 or 20 cc. Luer syringe in an upright position in a jar. Pour into it the clot, forcing it with the plunger through the nozzle into a bottle containing 15 cc. of semisolid agar. Inoculate 2 blood-agar plates and make a film preparation from the drop of blood remaining in the tube. Incubate one plate in the presence of 5 to 10 per cent CO_2 and the other anaerobically Stain the film with aqueous alcoholic methylene blue.

When blood containing an anticoagulant is examined, distribute 5 to 10 cc. of the blood in each of 2 bottles containing 50 cc of semisolid agar, 1 to 2 cc. in a tube of glucose-beef infusion agar for a poured plate, and a few drops to the surface of each of 2 blood-agar plates. Unless the examination is undertaken immediately after collection of the specimen, stain slide preparations with methylene blue. If large numbers of microorganisms are present, the Gram stain may also be helpful. Incubate one of the blood-agar plates anaerobically and the other in the presence of 5 to 10 per cent CO_2.

To distribute a specimen received in a Keidel tube or other container with a constricted opening, draw the blood into a capillary pipette or a 20 cc syringe fitted with a 17 or 19 gauge needle.

If arrangements can be made to have medium inoculated directly after collection of the blood with a syringe, use 100 cc bottles fitted with bakelite screw caps and rubber diaphragms and containing 80 cc. of semisolid agar. After removing the cellophane cap, puncture the rubber diaphragm with the needle and force 5 to 10 cc. of blood into the bottle. Withdraw the needle, mix the blood and medium by rotating, and incubate as soon as possible.

Examine semisolid-agar inoculated with blood after incubation for twenty-four to forty-eight hours If no growth has been obtained on the original plate, make another set and a film from the semisolid-agar. Replate at the end of the first week and at the end of the month unless growth has occurred previously Incubate all plates for at least seven days

If specimens of other material to be cultured are not contaminated, the same procedures as for blood are used. Otherwise, "tests appropriate to the type and condition of the material" are employed

(For special technic of culture of spinal fluid, prostatic fluid, bile, stool, according to methods described by others, see page 305.)

Animal Inoculation

Gilbert [256] stated that cultural examination is preferable to animal tests for the demonstration of *Brucella* in blood. On the other hand it has been demonstrated that under some circumstances *Brucella* may be recovered only through animal inoculation. The procedure is almost prohibitive in cost, time, and space required and therefore should be reserved for those cases in which it is essential for proof of diagnosis of brucellosis itself or of a localization of infection

Poston [537] described a technic for animal inoculation which was sometimes successful when other methods failed. It differed from the methods then in use in that the animals were kept until specific reactions indicated *Brucella* infection. Beginning two months after inoculation, tests for specific agglutinins and for reaction to Brucellergen were made at intervals of a few days. When both reactions became positive the animals were killed, the animals which maintained negative agglutination and intradermal reaction were kept for four and a half months before sacrifice. (The advisability of repeated skin testing of animals in which agglutinins are being sought is questioned because of production of agglutinins by skin testing and possible sensitization of the animals.)

The technic in use at the Division of Laboratories and Research of the New York State Department of Health [649] is as follows:

> Intraperitoneal injection of 2 to 5 cc. of blood to which an anticoagulant has been added, or of clotted blood comminuted and suspended in salt solution, is made into a 250–300-Gm guinea pig If the animal is alive at the end of eight weeks, 1 to 2 cc. of blood is removed from the heart and the serum tested for agglutinins with an alcohol-treated suspension of *Brucella abortus*.
>
> If a reaction occurs, the guinea pig is chloroformed and autopsied If no agglutination is obtained, the animal is kept under observation and bled at intervals of two to four weeks If no agglutination occurs in blood procured four or five months after inoculation the animal is killed and autopsied.

Stained preparations and cultures on blood-agar slants are prepared from any apparent foci and from the heart's blood, spleen, liver, bile, and urine. Bile and urine is aspirated with syringes and hypodermic needles. The gross abnormalities in infected guinea pigs may be limited to a slight enlargement of the spleen which is often studded with caseous nodules. Lymph glands are frequently enlarged. Other foci may develop including inflammatory lesions in the region of the joints.

Precautions recommended against the spread of infection among inoculated animals are: Such animals are kept in isolation cages with deep trays, metal boxes, or glass jars in rooms preserved for the purpose. [Screened boxes or jars set in shallow trays containing water and sufficient kerosene to form a film on the surface may be a good precaution in view of the possible transmission of *Brucella* by insects.] When handing such animals, rubber gloves are worn and sterilized after use by 5 per cent cresol compound.

After necropsy, the animal is wrapped in several thicknesses of heavy paper, together with the wooden board used as an autopsy tray, and placed in an incinerator. Boxes or jars occupied by the animals, together with the bedding, water bottles, etc., are autoclaved. Animals that survive the test are chloroformed and disposed of similarly.

Carpenter [113] used shorter periods of observation of guinea pigs before sacrifice. If agglutinins appeared in the blood of the guinea pig two or three weeks after injection a postmortem examination was made. If no agglutinins were present he retained the animal for another two weeks before autopsy, and an agglutination test on the blood was repeated. Typical lesions of brucellosis seen in the guinea pig were enlarged joints and lymph nodes, splenomegaly, and necrotic foci in the liver. In the male animal a purulent seminal vesiculitis and epididymitis, with resulting atrophy of the testes, was commonly seen. Pure culture of *Brucella* could usually be isolated from the spleen, liver, lymph nodes, or any tissues that showed evidence of the disease. *In many instances the tissues of the guinea pig appeared normal, especially if they had been infected with* Brucella abortus, *therefore, cultures were made from the spleen and liver, even though no lesions were*

observed. Brucella suis caused more extensive lesions in guinea pigs than *Brucella melitensis* or *abortus.*

SPECIAL CULTURAL TECHNICS

Castañeda, Tovar, and Velez [133] reported an impressive increase in positive cultures as cultural methods were improved. In liver infusion broth they obtained cultures in 21 of 46 bloods (45 6 per cent), in 4 per cent sodium citrate solution 67 of 85 blood cultures were positive (78 8 per cent), and in bacto-tryptose broth 66 of 81 bloods yielded the organism (81.4 per cent). They obtained positive blood cultures in 150 of 200 patients studied, attributing their success, at least in some degree, to the care taken in subculturing So high a percentage of positive cultures undoubtedly also was partly attributable to the fact that the majority of the infecting strains were *Brucella melitensis* rather than *abortus* Wise and Kerby [117] modified this technic, obtaining a higher percentage of positive cultures but stated that an ideal method for culturing *Brucella* is yet to be devised. Their preference was for bacto-tryptose broth, with beef infusion broth as their second choice, liver infusion media was inadequate.

Castañeda [131] later described a simplified method for blood culture which he found very satisfactory after a trial period of six months·

A rubber-stoppered bottle of 4-, 6-, or 8-ounce capacity, containing sufficient 4 per cent bacto-tryptose agar to form a suitable slant along the side of the bottle, is autoclaved. After the agar has cooled and hardened, lying on its side, 5 to 20 cc. of equal parts of 2 per cent sterile sodium citrate solution and bacto-tryptose broth are introduced through the rubber stopper. Blood, freshly collected, in an amount equal to the citrate-broth content of the bottle, is introduced under rigid sterile precautions The bottle is turned on its side so that the contained agar slant is thoroughly moistened with the blood-citrate-broth mixture and is then stood upright in the incubator. Every forty-eight hours the bottle is turned on its side so as to again allow the blood-citrate-broth mixture to bathe the agar slant and then is again turned upright in the incubator. Colonies of *Brucella* may appear in

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was employed in the author's laboratory. All were patients with chronic brucellosis with low-grade or no fever, in whom *Brucella* septicemia was an unlikely possibility In 41 of these patients cultural attempts were made simultaneously in a fully equipped laboratory using standard methods for the isolation of *Brucella*, usually including animal inoculation, with no growth of *Brucella* resulting *

Lymph Node

The following technic for the isolation of *Brucella* from lymph nodes was described by Poston and Parsons [539]

Lymph nodes removed by biopsy are cut immediately into small pieces with sterile scissors and macerated in a sterile tissue press. Pieces of glands, or small amounts of tissue juice, are streaked over the surface of 2 liver infusion blood-agar, or North's gelatin blood-agar slants or plates. One culture is incubated in an atmosphere of 10 per cent CO_2 If slants are used the upper portion of the tube is heated in the flame to expel the air which is then replaced by blowing the breath into the tube through a sterile plugged pipette, and inserting immediately a sterile rubber stopper By this procedure concentration of approximately 10 per cent CO_2 is obtained

A Spray dish may be used for the incubation of the culture under increased CO_2 tension To a tube of molten liver infusion, or North's gelatin agar (cooled to 40° C) 2 cc of sterile sheep blood is added The blood mixture is poured into the top of the Spray dish and allowed to harden The lymph node material is then streaked over the surface of this medium. One cc of a molar solution of sodium bicarbonate is put into one side of the base of the dish and 1 cc of sulphuric acid (1 cc concentrated sulphuric acid to 29 cc distilled water) in the other side The dish containing the inoculated medium is placed over the base and sealed with paraffin After the paraffin has hardened completely the dish is tilted gently so that the alkaline and acid solutions are mixed

* Ultimately, when better technic for introduction of measured amounts of CO_2 was employed, *Brucella abortus* was isolated from the blood of 2 patients, in spite of negative results in institutional laboratories The method deserves additional trial

twenty-four to forty-eight hours or may require seven days or longer (*Fig.* 38). They are kept under observation for twenty-one days. When attempting blood culture in the chronic phase of brucellosis, Casta-



Fig 38 Castañeda technic for blood culture Growth of *Brucella abortus* visible over upper third of tryptose agar slant

ñeda stated that he thought it advisable to use a bottle of about 16-ounce capacity, containing about 50 cc of the citrate-broth-mixture, to which 50 cc. of the patient's blood is added.

The success of this method seems to depend upon maintenance of a proper CO_2 content of the bottle, if *Brucella abortus* is to be recovered. Failure of the method to produce growth of *Brucella* from the blood occurred in each of 58 instances in which it

melitensis in pure culture. Bruce[86] previously reported the organism in the feces of man, without attempting to culture it.

Isolation of *Brucella* from feces was described by Amoss and Poston[15] as follows:

About 1 Gm of fresh feces was mixed in 50 cc. of sterile isotonic salt solution and shaken for a few minutes to insure thorough suspension The suspension was filtered through 4 layers of #1 hospital gauze to remove gross particles and centrifuged at high speed for three minutes to throw down other particles and larger bacteria. To the supernatant suspension, a sufficient amount of immune serum was added to make the total dilution 1·100 and, after shaking, the mixture was placed in a 37° C. water bath for two hours The suspension was centrifugated at half-speed for five minutes and the supernatant fluid discarded. The precipitate was resuspended in isotonic salt solution, stirred, and centrifugated at the same speed again The supernatant fluid was again discarded and the procedure repeated twice Finally the precipitate was spread with a bent glass rod on eosin-methylene blue plates, some of which were incubated at 37° C aerobically and others in an anaerobic jar containing 10 per cent CO_2 Large clear colonies appeared after ninety-six hours These were fished and the organisms identified in the usual manner. In 20 experiments the patient's own serum known to agglutinate *Brucella melitensis*, strain 428 of the Hygienic Laboratory, was used to concentrate the fecal specimens. In 16 experiments, the polyvalent anti-*melitensis* serum produced by Mulford was employed in a dilution of 1 100 and of 1 300 with equal success. It is suggested, that in cases in which the organism has not been recovered from the urine or the blood but in which the patient's serum agglutinates members of the *Brucella* group, either the patient's serum or the corresponding polyvalent serum or monovalent serum be used On account of the dilution employed, the small amount of preservative may be disregarded

Parallel cultures by this method and by the usual planting on eosin-methylene blue plates resulted in the recovery of the organisms from 20 daily consecutive specimens of stool by the former method and in none by the latter method.

They pointed out that it is probable that the members of the

The culture is examined daily for the first evidence of growth of tiny colonies resembling droplets of moisture which may appear after 48 to 72 hours incubation. Stained smears from those colonies show minute coccoid bodies with indefinite outline which are difficult to distinguish from protein detritus from the original lymph node. Transplants are made to fresh media every two to three days after the first seventy-two hours incubation, even though there may be no visible growth *Brucella* will not grow on dried agar, unless transplants are made to fresh, moist medium, the colonies will not increase in size and the organisms will disappear. After 1 or 2 transplants, the colonies are larger and stained smears show the characteristic coccoid or bacillary form. The bacteriostatic action of dyes and agglutinin-absorption tests are used to differentiate the species of *Brucella*.

The cultures are supplemented by animal inoculation. The remaining portion of the lymph node is ground in a sterile mortar to which is added 2 cc. of sterile physiologic saline solution. One cc. of this mixture is injected subcutaneously into the groin of each of 2 guinea pigs, or intraperitoneally into each of 2 mice. The animals are kept for three months, if necessary, before they are killed The spleen, liver, peritoneal fluid, and lymph nodes (if enlarged) of the animals are cultured for *Brucella*

Lymph nodes from 19 patients with Hodgkin's disease have been cultured, and nodes from 10 of these patients yielded positive cultures of *Brucella*. *Brucella melitensis*, variety *suis*, was isolated 7 times and *Brucella melitensis*, variety *melitensis* in 3 instances (See page 273)

Brucella may be isolated from lymph nodes, providing the medium used is moist, not alkaline in reaction and that frequent transplants are made to fresh media Recently, North's gelatin agar has been used in addition to liver infusion agar and has been found to be quite satisfactory

Feces

Brucella organisms were first isolated from feces by Eyre [207] by emulsifying in saline some of the growth obtained on plates seeded with feces from a fatal case of Malta fever, precipitating the organisms by the addition of agglutinating serum, and again plating the sedimented microorganisms, thus obtaining *Brucella*

Spinal Fluid

One cc of a 1:100 dilution of inactivated polyvalent anti-*Brucella* serum was mixed with 5 cc. of the spinal fluid and incubated for one-half hour. The spinal fluid mixture was then centrifuged at a high speed for three minutes and the sediment planted on liver infusion blood agar slants and grown at 37° C. under increased CO_2 tension. To accomplish the latter, the upper portion of the test tube is heated in the flame to force out the air, the expired breath of the bacteriologist was blown into the tube through a sterile, plugged pipette and a rubber stopper immediately inserted Growth appeared in tubes inoculated from the mixture of spinal fluid and serum within twenty-four hours, whereas cultures of the untreated spinal fluid, some of which were centrifuged, showed no growth on the same medium until after seventy-two hours.

Prostatic and Seminal Vesicular Fluid

The technic of collecting prostatic and seminal vesicular secretions for culture was described by Boyd: [126]

The patient voids, almost but not quite emptying his bladder The urethra is then filled with a 1:1000 solution of acriflavine, using care not to permit the solution to enter the posterior urethra After enveloping the penis in cotton, soaking wet with acriflavine or cyanide of mercury solution, the acriflavine is permitted to ooze out of the urethra into the cotton After fifteen to twenty minutes and with the penis still protected by the cotton, the prostate and seminal vesicles are massaged wih pressure directed in such a fashion as to make the secretion enter the bladder A sterile catheter is then passed, and the first urine to flow out of the catheter, which may contain some acriflavine, is saved for microscopic examination, and the cultures are made from the remainder

OPSONOCYTOPHAGIC TEST

The work of Metchnikoff [477] in 1901, elaborated by others,[123–7, 622, 653, 728] formed the basis for practical application of the

Brucella group occur in large numbers in the stool, but that growth on artificial mediums is at first slow. By the usual planting method on eosin-methylene blue plates, the normal intestinal flora overgrow the *Brucella* organisms. When the organisms are clumped with immune serum, the colonies become apparent earlier than when single organisms are planted.

Few laboratories employ this technic, apparently looking upon culture of feces for *Brucella* as virtually impossible.

Bile

Isolation of *Brucella* from bile was described by Amoss and Poston,[14] using similar technic to that described for isolation of *Brucella* from stool specimens. They were the first to report isolation of *Brucella* from bile obtained by duodenal drainage.

Blood Clot

Using media devised by Selleis and Morris [619] and by Bohls and Schuhardt,[67] modified by the substitution of from 0 2 to 2 per cent tryptose for peptone and the elimination of glycerine, and by the addition of *p*-aminobenzoic acid, Jordan and Borts [384] cultured blood clot as follows.

> After centrifugation, the serum is drawn off with a capillary pipette *under rigid asepsis The clot is poured carefully into a tube of tryp*tose-bile medium. Clot cultures are incubated under 10 per cent carbon dioxide and sub-cultured to tryptose slants weekly for three weeks before being discarded as negative [Longer periods of subculturing are desirable (p 297)]

Recovery of *Brucella* from blood kept at room temperature for three years, by inoculation in liver infusion agar was reported by Ithurrat [373] He stated that blood clot should always be cultured in a liquid medium

Use of autoclaved syringes and needles in the collection of blood from which the clot may be used for culture, to avoid contamination of the specimen with spore-forming and other bacteria, was recommended by Jordan and Borts [384]

Capillary pipettes, finely drawn tip, rubber bulbs attached
Agglutination tubes, approximately 11 × 25 mm.
Five or ten cc. Luer syringes
Test-tube racks
Bacto-tryptose agar, dehydrated (Difco)
Slides
Cover slips
Vials, capped or corked, of approximately 10 cc. capacity for citrated blood
Platinum loop
Sodium citrate, 20 per cent solution in normal saline
Hastings' stain
Bunsen burner
Gates apparatus, or a silica turbidity standard (300 parts per million of silica in an 8 cc homeopathic vial, sealed with paraffin to prevent deterioration), or McFarland nephelometer, tube 16

The following technic is that of Huddleson,[366] with modifications suggested by Evans [203] and the author:

In preparation for the test, *Brucella abortus* organisms (strain #322 or other virulent laboratory strain of smooth *Brucella abortus*) are transferred to a bacto-tryptose agar slant and the slant incubated for forty-eight hours at 37.5° C., and then refrigerated for not more than eight hours before use (Since only 48-hour growths are used, appointments for the test must be made two days in advance or fresh transfers must be made daily so that a 48-hour-old culture is always at hand) It is essential that the strain used be smooth (not dissociated). Frequent examination of cultures for variants and contaminants are necessary (p 32).

Before performing each group of tests a fresh bacterial suspension is made by suspending loopfuls of *Brucella* organisms from the 48-hour slant in 3 to 5 cc. of 0 85 per cent sodium chloride solution in distilled water, until density matches tube 16 of the McFarland nephelometer (This is approximately the density of 1 cc on the Gates apparatus If the silica standard is used, 0 2 cc of the dense bacterial suspension is placed in an 8 cc. homeopathic vial and sterile physiologic saline is added until the density matches that of the standard)

Sterile capped or stoppered homeopathic vials are prepared and

measurement of the phagocytic power of the white cells to the study of brucellosis.[384, 309] The test is based on the ability of the polymorphonuclear leukocytes to phagocytize *Brucella* organisms. The degree of phagocytosis is a relative but not infallible measure of the patient's resistance to *Brucella* infection.

G. B. Shaw (*The Doctor's Dilemma*, 1906) put into concise words a still acceptable concept of the reaction. Ridgeon said: "Opsonin is what you butter the disease germs with to make your white blood corpuscles eat them." Sir Patrick replied: "I heard this theory that the phagocytes eat up the disease germs long ago: long before you came into fashion. Besides, they don't always eat them." Ridgeon insisted that they do "when you butter them with opsonin."

Evans[203] stated that the opsonocytophagic test is the least informative of the individual diagnostic measures When the information is properly correlated with that of the other laboratory procedures, the significance of the opsonocytophagic test becomes greater This concept has been confirmed by Evans as essentially in agreement with her own.

Wise[714] considered the test specific in that an individual's blood which phagocytes *Brucella* does not phagocyte other organisms to any considerable degree. The observations of Foshay and Calder[235] (p. 279) also tended to show that the reaction, in conjunction with other noncultural methods, is specific.

The evaluation of the test will be discussed following consideration of technical details.

Technic

Apparatus needed:

Microscope, with mechanical stage
Incubator (accurate within one degree)
Autoclave
Refrigerator
Wire-mesh covered pan or other simple device for use in staining films
Pipettes, 1 cc, graduated in 0 1 cc.

(Figure 39 illustrates varying degrees of phagocytosis.) The number of cells showing marked, moderate, slight, or no phagocytosis is then recorded

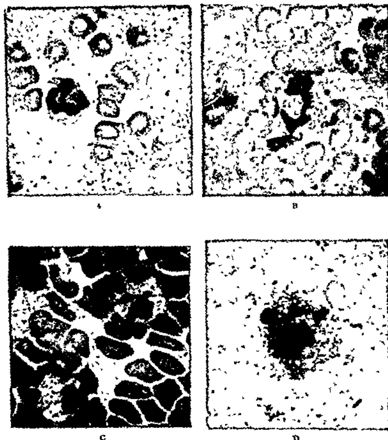


Fig 39 Degrees of phagocytosis (After Huddleson) A No phagocytosis B Slight phagocytosis C Moderate phagocytosis D Marked phagocytosis

The bacteria within each cell are actually counted, unless the cell is so filled with organisms that accurate counting is impossible Under these circumstances it is safe to assume that it contains more than 40 organisms

0.2 cc. of sterile 20 per cent sodium citrate in normal saline is added to each. This is sufficient to prevent clotting and to produce a citrate concentration of 0.8 per cent when 5 cc. of blood are added.

Blood is collected and exactly 5.0 cc. placed in a vial containing the 0.2 cc. of 20 per cent sodium citrate in normal saline, and the vial gently agitated or inverted to insure thorough mixture. Both blood and citrate must be measured accurately. (The blood specimen should not be more than three hours old [p. 321].)

One-tenth of 1 cc. of the bacterial suspension is placed in an agglutination tube, to which is added 0.1 cc. of the citrated blood, and thoroughly agitated by shaking. The citrate concentration in the blood is now 0.4 per cent.

The tube containing the bacterial suspension and citrated blood is incubated for thirty minutes at 37.5° C.

With a capillary pipette a sufficient quantity of the mixture is withdrawn to make several cover slips or slide films. The technic is the same as that used in making blood films for differential counts. Rapid drying is essential; the films may be placed in the stream of an electric fan or waved briskly in the air.

Films may be found to stain satisfactorily if the Hastings' stain is not diluted at the end of forty-five seconds, in accordance with the usual technic, but allowed to remain undiluted for three minutes and then washed with distilled water, allowed to dry, and mounted in balsam. Or the film may be stained for thirty seconds, diluted with distilled water, and allowed to stand for one minute, then washed. Evans expressed preference for Bordet-Gengou's carbol toluidin blue.

For the expert technician examination of 25 polymorphonuclear leukocytes in various parts of the film under the oil-immersion objective results in accurate readings. (Until expertness is achieved, examination of 100 cells is recommended.) Each cell is classified as showing:

- Marked phagocytosis when 41 or more bacteria are seen within the cell
- Moderate phagocytosis when from 21 to 40 bacteria are seen within the cell
- Slight phagocytosis when from 1 to 20 bacteria are seen within the cell
- No phagocytosis when 0 bacteria are seen within the cell

Foshay and Le Blanc [241] (Table VIII) devised a means of using a nomogram to arrive at a numerical index from numbers of cells showing the various degrees of phagocytosis, making it unnecessary to record the entire reading routinely. The index number represents an approximate expression of the patient's immediate capacity to phagocytose *Brucella* expressed in percentage of total potential capacity.

Recording

Recording of the actual number of cells showing marked, moderate, slight, and no phagocytosis, seems preferable to use of percentage of cells in each category, because of greater simplicity. It must be stated in reporting on phagocytosis whether cells showing marked phagocytosis are recorded in the first or fourth column. A reading such as 0–0–10–15 would give a Foshay index of 90, a high degree of phagocytosis; if reversed by placing cells showing marked phagocytosis in the first column, without so stating, it would be computed as 10, representing a negligible degree of phagocytosis (This point is elaborated in subsequent pages.)

The author records marked phagocytosis in the first column and no phagocytosis in the fourth and arrives at a numerical index by a simpler method devised with the aid of Dr DeWitt H. Smith, without recourse to the Foshay nomogram, although inspired by it By this modification the number of cells showing marked phagocytosis is multiplied by 4, those showing moderate phagocytosis by 3, and those showing slight phagocytosis by 1, those showing no phagocytosis are ignored. The sum of the products of multiplication of the first three columns in the numerical index, which corresponds exactly to the index as computed by the Foshay nomogram Examples are given on page 318

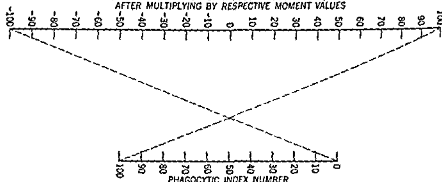
The number of cells showing each degree of phagocytosis and those cells showing no phagocytosis is expressed in percentage by some workers Others report only the number or percentage of cells showing marked phagocytosis. Still others report in terms of numbers (or percentage) of cells as "positive," i e., showing

Old polymorphonuclear leukocytes, in which the nuclei-connecting filaments have disappeared, should not be considered since they do not ingest organisms (Huddleson).

Evans pointed out that it is not the number of bacteria which appear to be within the leukocyte that is important but rather whether these bacteria are more numerous than in an equivalent area of the surrounding field.

TABLE VIII

CALCULATION OF PHAGOCYTIC NUMBERS



Nomogram for the conversion of inclusion counts into phagocytic index numbers The algebraic sum of the weighted inclusion count frequencies is located on the -100 to $+100$ scale A straight edge from this point, passing through the central black dot, intersects the smaller scale at a point where the phagocytic index number may be read off directly

For the use of this conversion method, Foshay and Le Blanc [341] recorded cells showing no phagocytosis in the first column, those showing slight phagocytosis in the second, those showing moderate phagocytosis in the third, and those showing marked phagocytosis in the fourth column. A total of 25 polymorphonuclear leukocytes were used in the count. The number of cells in the first column was multiplied by -4, those in the second column by -2, those in the third by $+2$ and those in the fourth by $+4$ For example

No bacteria within each cell (no phagocytosis)	*1-20 bacteria within each cell (slight phagocytosis)*	*21-40 bacteria within each cell (moderate phagocytosis)*	*41 or more bacteria within each cell (marked phagocytosis)*
6 cells	9 cells	3 cells	7 cells
$\times -4 = -24$	$\times -2 = -18$	$\times +2 = +6$	$\times +4 = +28$

The sum of the four products is -8 in the -100 to $+100$ range, corresponding to 46 on the final base line The phagocytic index number is therefore 46.

The opsonocytophagic reaction performed on the blood specimen of ——, on ——, showed:

Marked phagocytosis in —— cells
Moderate phagocytosis in —— cells
Slight phagocytosis in —— cells
No phagocytosis in —— cells

This reading represents a numerical index of ——, and indicates

no
slight
moderate
marked
} resistance

to *Brucella* infection at the time the test was performed Interpretation should be made in the light of other laboratory and clinical data

Sources of Error

1. *Dissociation of the strain of live* Brucella *organisms used* Rough strains are likely to result in high degrees of phagocytosis in any sera tested. The smoothness of the strain being used must be determined at frequent intervals (p 32)

2. *Use of encapsulated strains of* Brucella Wise[714] found that greater phagocytic activity occurred against nonencapsulated laboratory strains of *Brucella suis* than against encapsulated strains isolated from a patient having Hodgkin's disease

3 *Use of killed* Brucella *organisms* Various workers have thought that suspensions of killed organisms are equally satisfactory as virulent live organisms[380] Others[235, 351] found that use of killed organisms gave inaccurate results Tovar[669] considered formalin-killed organisms suitable. In the author's laboratory it was found that lower average readings resulted from the use of formalin killed organisms The average of the indices using live organisms was 32 9, the average of the indices using formalin-killed organisms 19 9 There was no practical difference between phenol-killed and formalin-killed organisms in their response to phagocytosis Huddleson[356] suggested that use of *Brucella abortus* killed by phenyl mercuric borate in a final dilution of 1 50,000 or 1 100,000 would give accurate results In an attempt to evaluate this method the opsonocytophagic test was performed on the blood of 79 consecutive patients, most of whom were suffering from chronic brucellosis, using a smooth strain of virulent live *Brucella*

Cells showing marked phagocytosis (41 or more bacteria within each leukocyte)	Cells showing moderate phagocytosis (21–40 bacteria within each leukocyte)	Cells showing slight phagocytosis (1–20 bacteria within each leukocyte)	Cells showing no phagocytosis (0 bacteria within each leukocyte)	Foshay numerical index	Modified Foshay numerical index
0(×4 = 0)	0(×3 = 0)	0(×1 = 0)	25(×0 = 0)	0	0
25(×4 = 100)	0(×3 = 0)	0(×1 = 0)	0(×0 = 0)	100	100
14(×4 = 56)	9(×3 = 27)	2(×1 = 2)	1(×0 = 0)	85	(56 + 27 + 2 = 85)
1(×4 = 4)	8(×3 = 24)	7(×1 = 7)	9(×0 = 0)	35	(4 + 24 + 7 = 35)

phagocytosis of any degree. Whereas accurate correlation with the other systems may be made if percentage of the various degrees of phagocytosis is recorded, no correlation is possible if only the percentage of cells showing marked phagocytosis or only the percentage of "positive" cells is recorded; for example:

Marked phagocytosis	Moderate phagocytosis	Slight phagocytosis	No phagocytosis	Foshay index	Modified index
5 cells (20 per cent)	16 cells (64 per cent)	4 cells (16 per cent)	0 cells (0 per cent)	72	72

If the above reading were reported as "20 per cent of the cells showed marked phagocytosis," the impression is given of only very moderate phagocytic activity. Cells showing moderate phagocytosis have almost as much significance as those with marked phagocytosis A reading such as 0–8–8–9 would be reported as "no cells showed marked phagocytosis," in no way distinguishing it from a very low reading such as 0–0–4–21, actually the former reading gives an index of 32, and the latter one of only 4

It is not intended to overstress the value of a numerical index, but rather to achieve sufficient uniformity so that reports from various laboratories may be comparable

Using this method, the report of the laboratory may be expressed as follows

The opsonocytophagic reaction performed on the blood specimen of ———, on ———, showed.

Marked phagocytosis in — cells
Moderate phagocytosis in — cells
Slight phagocytosis in — cells
No phagocytosis in — cells

This reading represents a numerical index of —, and indicates

no
slight
moderate
marked

} resistance

to *Brucella* infection at the time the test was performed. Interpretation should be made in the light of other laboratory and clinical data

Sources of Error

1. *Dissociation of the strain of live* Brucella *organisms used* Rough strains are likely to result in high degrees of phagocytosis in any sera tested The smoothness of the strain being used must be determined at frequent intervals (p 32).

2. *Use of encapsulated strains of* Brucella Wise[714] found that greater phagocytic activity occurred against nonencapsulated laboratory strains of *Brucella suis* than against encapsulated strains isolated from a patient having Hodgkin's disease

3. *Use of killed* Brucella *organisms* Various workers have thought that suspensions of killed organisms are equally satisfactory as virulent live organisms[780] Others[255, 351] found that use of killed organisms gave inaccurate results Tovar[663] considered formalin-killed organisms suitable In the author's laboratory it was found that lower average readings resulted from the use of formalin-killed organisms The average of the indices using live organisms was 32 9, the average of the indices using formalin-killed organisms 19 9 There was no practical difference between phenol-killed and formalin-killed organisms in their response to phagocytosis Huddleson[356] suggested that use of *Brucella abortus* killed by phenyl mercuric borate in a final dilution of 1 50,000 or 1 100,000 would give accurate results In an attempt to evaluate this method the opsonocytophagic test was performed on the blood of 79 consecutive patients, most of whom were suffering from chronic brucellosis, using a smooth strain of virulent live *Brucella*

abortus organisms, and organisms of the same strain and in the same density killed by phenyl mercuric borate in each. Slightly lower individual and average readings were found using organisms killed by phenyl mercuric borate as compared with live organisms. The average of the indices using live organisms was 44; the average of the indices using phenyl-mercuric-borate-killed organisms was 36.8. If these observations are verified, use of *Brucella* organisms killed by phenyl mercuric borate may prove to be a satisfactory substitute.

4. *Use of varying concentrations of live* Brucella *organisms.* Wide variations in phagocytic activity will result from relatively slight variations in the number of live organisms in the suspension used. The following variations were noted:

McFarland nephelometer reading	*Average phagocytic activity in 9 sera*
8	24 1
16	28
20	40.5

A reading of 16, as recommended by Huddleson, has been adopted as standard.

5. *Use of varying concentrations of sodium citrate.* Phagocytosis is inhibited by sodium citrate in increasing concentrations The amount used should be sufficient to prevent clotting but not sufficient to inhibit phagocytosis Huddleson found a citrate content of 0.8 per cent to serve the purpose (0 2 cc of sodium citrate in 20 per cent normal saline added to 5 cc. of blood). Tovar * stated that 2 per cent of citrate inhibits "normal" opsonins and has no inhibitory effect upon the specific opsonins In a series of 27 tests made on blood of patients known or suspected to be suffering from chronic brucellosis, marked inhibition of phagocytosis was noted in the use of 2 per cent sodium citrate concentrations as compared with 0 8 per cent citrate concentration.

Using a final concentration of 0 4 per cent (Huddleson), the average index was 54 3, using a final concentration of 1 0 per cent (Tovar), the average index was 31 3. Use of the 0 8 per cent citrate concentration

* Tovar included observations on "normal" persons as a control It is questionable how a selection of "normal" (uninfected) persons can be made since freedom from symptoms of brucellosis does not exclude latent or mild infection The finding of opsonins in the blood of a well person does not signify that they are "normal" opsonins

seems preferable, to avoid suppression of significant phagocytosis and for the sake of standardization

6 *Use of various species of* Brucella. Many laboratories perform the test using *abortus, suis,* and *melitensis* separately. Some variation in phagocytosis against the various species is reported. Only slight variations have been noted by the author and others [203, 351] *Brucella abortus* seems preferable for the sake of standardization and because it constitutes less of a menace to technicians than the more virulent *suis* and *melitensis* strains

7. *Time interval between collection of the specimen and performance of the test* Most specimens maintain a fairly constant phagocytic activity for five or more hours (some as long as twenty-four hours) at room temperature. However, variable results are found in a sufficient number of specimens after standing for three hours to indicate the importance of performing the test within three hours or less after collection.

In approximately one-fourth of the specimens, there was significant reduction in phagocytic activity at the end of five hours, making the interpretation difficult or worthless In one specimen there was marked lessening of phagocytosis in three hours

Borman [70] considered it inadvisable for a central laboratory to perform the test as a control upon treatment because of the variable time factor between collection of the specimen and start of examination He stated that broad interpretations may be made when results are correlated with the skin test, but finer interpretation may be misleading The author's experience suggests the advisability of fresh specimens even in the diagnostic use of the test.

8 *Methods of staining* Hastings' stain is used in the author's laboratory Wright's stain is used by many. Huddleson expressed preference for the Calmette-Negre-Boquet stain when *melitensis* infection is involved, as in Malta, because the leukocytes are likely to contain large numbers of pseudobasophilic granules which may closely resemble organisms, the organisms but not the granules are stained by this method

Evans preferred the Bordet-Gengou carbol toluidin blue method. In this method thick blood films are treated with 1 per cent acetic acid and 5 per cent formalin in distilled water to dissolve the red cells before staining. Stevenson, working in the author's laboratory, con-

sidered the method inferior to routine Hastings' staining method, but an associate produced excellent slides with deep staining of nuclei and bacteria on a clear background, without shrinkage.

Inexperienced workers may mistake precipitated stain for *Brucella* organisms. Other errors include overstaining which blots out the organisms within the leukocytes.

9. *Variation in readings made by different technicians.* The organisms contained within each cell can and should be counted to determine slight and moderate degrees of phagocytosis. In cells containing more than 40 bacteria it may be impossible to do more than establish that fact When the technician simply estimates the number of ingested organisms, errors are likely, particularly when the numbers of organisms are borderline, such as about 20 or about 40 If estimated as 18 a cell would be placed in the category of slight phagocytosis, if actually counted and found to be 21, the cell would be listed among those showing moderate phagocytosis The distinction between "moderate" (21 to 40 organisms per cell) and "marked" (41 or more organisms per cell) is even more important It is a good precaution to have different workers in the same laboratory standardize technic by checking each other's slides at intervals. Borman [70] remarked that "it is very easy for the observer to overestimate or underestimate the number of organisms in a given cell when pushed for time and I suspect that some will always overestimate while others will underestimate"

Interpretation

Huddleson stated that an individual is classified as susceptible if the skin test is negative and the phagocytic index low or "negative" as infected if the skin test is positive and less than 40 per cent of the cells show marked phagocytosis, as questionably infected or immune if 40 to 50 per cent of the cells show marked phagocytosis, and as immune if 60 per cent of the cells show marked phagocytosis This evaluation is subject to modifications in the practical application of the test

The number of cells showing marked, moderate, and slight phagocytosis furnishes a direct, although rough, index of the patient's resistance to *Brucella* infection, in the aggregate. In successive tests, the shift from "slight" to "moderate" and from "moderate" to "marked," indicates an increasing phagocytic power of

the white cells and therefore an increasing immunologic response.

The usefulness as well as the limitations of the test may be clarified by the following observations, based on application of the test, in diagnosis and as a criterion of progress while under treatment, in over 500 patients observed for periods of from one to twelve years. An attempt is made to reconcile these observations with those of others.

The test is largely a quantitive one, showing the measurable degree of resistance to Brucella *infection.* Ordinarily it should not be considered as "positive" or "negative" (Some qualitative conclusions may be drawn from it under circumstances to be set forth subsequently but it may not safely be used to establish a diagnosis when "positive" or to rule out brucellosis if "negative") If referred to as a "positive" reading the impression is given, often erroneously, that the patient is ill with brucellosis As will be shown, a "positive" reading may be found in the presence of active illness, in the absence of active illness (in patients who have recovered), or in response to skin testing or therapeutic doses of *Brucella* antigens.

According to Wise [714] a positive index may be illustrated by marked phagocytosis in 0 cells, moderate phagocytosis in 5 cells, slight phagocytosis in 15 cells, and no phagocytosis in 5 cells (0–5–15–5, a numerical index of 30) or by any higher degree of phagocytic activity According to Huddleson an index of 0–0–6–19 (a numerical index of 6) or higher may be considered "positive." The discrepancy in viewpoint is explained by the fact that Wise considered that the blood of "normal" individuals may exhibit sufficient phagocytic activity of *Brucella* organisms to give numerical indices as high as 30 This concept may be accurate, although it is impossible to be certain that the "normal" individuals have not had remote or recent *Brucella* infections, resulting in continued presence of opsonins

A "negative" reading may be found in the presence of active infection (as proved by culture), indicating lack of phagocytic response to infection, or in patients who have recovered, or in patients who, presumably, never have been infected

The reaction must be interpreted in the light of the other laboratory procedures—skin test, agglutination test, and culture—and in relation to the clinical status of the patient.

There is no definite correlation between active Brucella *infection and phagocytic activity of the white cells.* If the terms "positive" and "negative" are avoided in recording the results of the test, inconsistencies no longer exist. A patient may be acutely or chronically ill, with proved *Brucella* infection, with a high or with a low index, depending entirely on his immunologic response. In the chronic phase of the disease low phagocytic indices are usual in patients in whom no *Brucella* antigens have been used, nature's attempt to combat the infection having failed.

There is no inconsistency in such findings as those of Morales-Otero and Gonzalez [197] if this concept is entertained. In one study they found 5 persons to have "positive" opsonocytophagic tests and negative cutaneous reactions; 18 persons had "negative" opsonocytophagic tests and positive intracutaneous reactions. The patients with opsonins but no cutaneous allergy presumably were or had been infected but had not developed skin allergy or had lost the skin allergy once present. The patients with no opsonins but with cutaneous allergy were or had been infected, and had not developed opsonins or had lost the opsonins once possessed. Their status would depend upon correlation of these findings with culture, agglutination test, clinical findings, and perhaps upon clinical and serologic response to therapeutic trial of specific vaccine.

For the reasons stated, the opsonocytophagic test is not of great value in case-finding. Whereas any degree of phagocytosis may be found in infected persons, absence of any phagocytic activity does not preclude infection.

Perhaps the most concise way in which this controversial subject can be expressed is as follows. *The opsonocytophagic test is not by itself a diagnostic test, but takes on diagnostic significance in the presence of other laboratory and clinical evidence of brucellosis. Furthermore, it is not a definitive criterion of immunity, recovery, or cure, but rather is a useful guide in assessing*

progress in patients treated with Brucella *antigens, in the presence of clinical evidence that points in the same direction.*

A hypothetical case, based on many similar ones, is quoted to illustrate the usual application of the test, diagnostically and prognostically.

A patient with symptoms suggesting chronic brucellosis (fatigue, sweating, myalgia, weight-loss, shifting arthralgia, and headache) presented no definite physical findings except moderate tender swelling of one knee joint Other routine study was unrevealing except for low-grade fever Blood-agglutination reaction with *Brucella abortus* was positive in a low dilution of the serum only (1:40) by the microscopic method and confirmed by the tube method There was a mild normocytic anemia with leukopenia and relative lymphocytosis Erythrocyte sedimentation rate was 36 mm in one hour (Westergren) Skin test was withheld pending further study Culture of synovial fluid from the hydrarthrotic joint, of blood, and of urine for *Brucella*, and animal inoculation, was initiated The opsonocytophagic reaction showed a slight degree of resistance, presumably in response to old or recent infection, active or inactive:

Marked phagocytosis	*Moderate phagocytosis*	*Slight phagocytosis*	*No phagocytosis*	*Numerical index*
0 cells	5 cells	9 cells	11 cells	24

Skin test, performed after collection of blood for the agglutination and opsonocytophagic reaction, was positive, indicating that the patient had, or had had, *Brucella* infection The blood-agglutination reaction, even in low titer, added some weight to the possibility of past or present infection The slight phagocytic reaction suggested that he had not recovered, in view of persisting symptoms referable to brucellosis The leukopenia with relative lymphocytosis was consistent with the tentative diagnosis The elevated sedimentation rate also was consistent with the joint manifestations.

The patient improved following therapeutic doses of *Brucella abortus* vaccine A month after the first series of tests, the phagocytic index was repeated, showing a reading of 5–9–11–0 If this reading is recorded below the first, the shift to the left is readily seen and interpreted as indicating increasing resistance to *Brucella* infection:

The reaction must be interpreted in the light of the other laboratory procedures—skin test, agglutination test, and culture—and in relation to the clinical status of the patient.

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patient was instructed to resume vaccine therapy for a period of about three months and then to report for further observation. When next seen the index was at a high level (19–6–0–0, a numerical index of 94) and the patient was symptomless. The test was repeated at gradually increasing intervals for the next two years and was found to fluctuate within a high range. Once, during the third year of observation, there was evidence of mild relapse accompanied by a fall in the index, following an intercurrent illness. He complained particularly of lameness of one shoulder and of fatigue. The clinical and serologic picture was reversed following three additional doses of *Brucella* vaccine and the patient remained well throughout the next three years of observation. It was considered that cure was not assured, but that possible recurrences could be controlled.

Maintenance of a high degree of phagocytosis may not be essential to lasting recovery in all patients; if the organism is eradicated phagocytosis may play no role beyond furnishing some protection against reinfection; if the infection is quiescent it may prevent exacerbation.

Children commonly recover and remain well in the presence of lesser phagocytic activity than usually is found important in adults.

In a small proportion of patients a sustained rise in the phagocytic index is not accompanied by subjective or objective evidence of improvement or recovery. Such a situation may be due to (1) error in diagnosis, (2) coexistence of other illness, (3) continued sensitization to *Brucella*, or (4) persistent localized *Brucella* infection causing exacerbation of illness in spite of supposedly adequate resistance.

Also in a small percentage of patients phagocytosis seems to play no role in recovery. In these patients, phagocytosis by fixed phagocytes (p. 330) may have taken up the burden of defense, other unknown mechanisms may be responsible, or desensitization alone may be the mechanism of recovery.

Marked phagocytosis	*Moderate phagocytosis*	*Slight phagocytosis*	*No phagocytosis*	*Numerical index*
0	5	9	11	24
5	9	11	0	58

The patient stated that he had felt better for the past several weeks, with lessening of sweats, arthralgia, low-grade fever, and fatigue. The swelling of the knee had subsided. Sedimentation rate was 22 mm Treatment was continued and the patient reported five weeks later for further observation He stated that he had felt well for the past two weeks. Sedimentation rate was 14 mm and blood count was normal. The third phagocytic index showed a reading of 16–9–0–0 Comparison with previous readings showed.

Marked phagocytosis	*Moderate phagocytosis*	*Slight phagocytosis*	*No phagocytosis*	*Numerical index*
0	5	9	11	24
5	9	11	0	58
16	9	0	0	91

The patient was told that the rise in his phagocytic index had paralleled his clinical progress and that the early tentative diagnosis of brucellosis had been strengthened to some degree. Treatment was discontinued with the advice that the phagocytic index was to be redetermined in about six weeks, or at any time in the interim if symptoms should recur Three months later the patient returned complaining that he had felt ill, with recurrence of various symptoms, for about a month Physical examination was negative save for a slight temperature elevation, and mild anemia and leukopenia with lymphocytosis Cultures had been reported as negative in the interim A fourth phagocytic index was 0–10–14–1, indicating an appreciable lessening of specific resistance Comparison with previous readings showed

Marked phagocytosis	*Moderate phagocytosis*	*Slight phagocytosis*	*No phagocytosis*	*Numerical index*
0	5	9	11	24
5	9	11	0	58
16	9	0	0	91
0	10	14	1	44

It was apparent that the phagocytic index had furnished a good criterion of progress and that symptoms recurred in the presence of lessening resistance (and perhaps with recurring sensitization) The

patient was instructed to resume vaccine therapy for a period of about three months and then to report for further observation. When next seen the index was at a high level (19–6–0–0, a numerical index of 94) and the patient was symptomless The test was repeated at gradually increasing intervals for the next two years and was found to fluctuate within a high range Once, during the third year of observation, there was evidence of mild relapse accompanied by a fall in the index, following an intercurrent illness He complained particularly of lameness of one shoulder and of fatigue The clinical and serologic picture was reversed following three additional doses of *Brucella* vaccine and the patient remained well throughout the next three years of observation It was considered that cure was not assured, but that possible recurrences could be controlled.

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Specificity of Phagocytosis

Specificity of phagocytosis has been mentioned (p. 279).

The author has noted no tendency of the phagocytic power of the white cells against *Brucella* to increase in the presence of other disease, such as has been reported [473] (p. 284). On the contrary, in patients with high phagocytic indices, intercurrent infection such as influenza or pneumonia usually caused a marked lowering of the phagocytic index.

Phagocytosis of *Brucella* in considerable degree was reported by Huddleson in 2 cases of active *B. tularense* infection. Also it has been shown (p. 331) that prophylactic use of cholera vaccine may produce phagocytic activity against *Brucella*.

Such nonspecific reactions may cause temporary confusion, especially if agglutinins as well as opsonins are so induced, emphasizing the need for use of the battery of tests and for their interpretation in the light of each other and of clinical evidence.

Over-indulgence in alcohol apparently has been responsible for marked lessening of phagocytosis in several of the author's patients.

"Positive" Opsonocytophagic Reactions

Under some circumstances the phagocytic index may furnish supportive diagnostic evidence of *Brucella* infection when other laboratory data are equivocal or lacking (p 252). In an untreated patient in whom no skin test has been performed, an index such as 0–6–15–4 (a numerical index of 33), or higher, suggests that the patient is either infected, with some immunologic response, or recovering from an active infection Clinical findings and other laboratory data must be utilized to clarify such an index. In that sense only does it seem proper to designate the reaction as "positive"

A skin test with any of the commonly used *Brucella* antigens or therapeutic doses of vaccine may so alter the phagocytic power of white cells as to render the test valueless as a diagnostic aid Phagocytic response may follow intradermal *Brucella* antigens within six days, perhaps in 48 hours or less (p 343).

Susceptibility to Infection

Susceptibility to infection, as evidenced by a low or "negative" phagocytic index and negative skin test has been a controversial subject. Huddleson noted that such persons were very susceptible to laboratory infection He considered it unsafe for laboratory personnel to begin working with the more virulent *melitensis* and *suis* strains until some resistance to infection to these strains had been built up through contact with *abortus* strains. It is doubtful that this applies to the general population, who are exposed to smaller numbers of less virulent organisms in dairy products. Among thousands of tests done by the author among urban and rural populations, representing occasional exposure in the former and frequent exposure in the latter group, a common infected milk supply did not result in clinical or laboratory evidence of infection in all users of such milk, although they had very low phagocytic indices and negative skin tests.

"Susceptibility" is a relative term in its practical application. Negative skin tests and low or "negative" phagocytic indices usually mean that infection has not occurred, but either or both may be found in the presence of positive culture.

Immunity

The question of immunity also is controversial. An immune status is attributed by Huddleson [351] to those persons whose phagocytic indices show a high degree of phagocytic activity (60 to 100 per cent of cells with marked phagocytosis), in the presence of a positive skin test. That this has practical importance as a protective mechanism was shown in laboratory workers exposed to virulent, massive infection That it does not indicate immunity, in the usual meaning of the term, or cure, or complete recovery, is shown by the not infrequent finding of active illness, positive blood culture, or positive culture from localized infections, in the presence of marked phagocytosis in all cells (a numerical index of 100) Robinson and Evans [580] reported the death of one patient whose blood showed a "very strong opsonocytophagic reaction"

In the absence of symptoms referable to brucellosis, a high degree of phagocytic activity in the presence of a positive skin test usually is evidence of at least a balance between infection and immunity. However, such patients may lose this degree of resistance at any time and may relapse if active infection persists. Allergy may persist in spite of marked phagocytosis.

Delafield and Prudden[172] stated: "The mere fact of phagocytosis is not evidence of successful protection, since the ingested bacteria may destroy the phagocyte at once, may possibly gain in its interior by adaptation of an exalted virulence, or may be transported to various parts of the body. The virulence of bacteria has an important bearing upon the effectiveness of phagocytosis. It has been found that the bacteria of high virulence are much less susceptible to phagocytosis than are the less virulent strains of the same species, both in normal and in immune sera. It would appear that virulent bacteria may be protected from phagocytosis both by their insusceptibility to opsonification and by their capacity to produce substances harmful to the phagocytes." Although immunity and desensitization usually are concomitant phenomena, sensitization may persist or recur in spite of immunity (pp. 455–461).

According to Zinsser and Bayne-Jones,[719] phagocytic cells may be divided into wandering cells (polymorphonuclear leukocytes or microphages, and certain large mononuclear elements or macrophages) and fixed cells. The macrophages and fixed-cell phagocytes are considered to be derivatives of the reticulo-endothelial system. Macrophages are distributed in the lining cells of capillaries, lymph sinuses, sinuses of the spleen and serous cavities, in reticular connective tissue, lymphatic tissue, thymus, Kupffer cells of the liver, and in the circulating blood. Phagocytosis of organisms in tissues is chiefly mononuclear and there seems to be an extraordinary mobility of clasmatocytes through tissues into areas of invasion.

This concept of phagocytosis in circulating blood and in tissues helps to explain the theory that phagocytosis as measured in the

polymorphonuclear cells alone is but one part of the system of phagocytosis by which protection is achieved.

The phagocyted organism may be destroyed by intracellular digestion or, failing that, it may bring about the death of the leukocyte which itself disintegrates [172, 359] This may explain why phagocytosis is not always a benign process and that active illness or even fatal termination of illness can occur in the presence of marked phagocytic power in all polymorphonuclear leukocytes.

Significance in Healthy Persons

The presence of high phagocytic power of the white cells in persons with no manifestations of *Brucella* infection probably does not indicate natural immunity. It is probable that such findings, in persons who have had no *Brucella* skin tests or *Brucella* vaccine therapeutically, indicate remote or recent infection with *Brucella*, perhaps localized and latent

Cholera vaccine given for prophylaxis was reported to produce marked opsonocytophagic reactions in 80 per cent of 20 persons by Eisele and his coworkers [191] Therefore, careful inquiry as to cholera prophylaxis should be made before interpreting either agglutination (p 285) or opsonocytophagic reaction

Maintenance of a high phagocytic index following apparent recovery from clinical brucellosis is discussed on pages 408, 458

INTRADERMAL REACTION

Fleischner and Meyer [223] described the cutaneous reaction to killed *Brucella abortus* organisms in 1918 Burnet [89] in 1922 made further observations using *melitensis* strains Giordano [262] in 1929 reported on the intradermal use of a saline suspension of heat-killed *Brucella abortus* organisms In 25 proved cases of brucellosis there were severe local reactions in all In 100 controls there were negative reactions in 99 per cent

Since these early observations much work has been done in an attempt to show the value and the limitations of various methods, using various fractions, filtrates, and whole organisms Too much importance may be attached to a positive reaction by some or to

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was suggested by the findings of Angle and his associates.[23] Cutaneous tests were performed on 163 inmates of an institution which was served with raw milk from an infected herd Brucellergen and heat-killed *Brucella* organisms were used concomitantly, in opposite arms. *There were 89 reactors to the heat-killed vaccine (54 6 per cent) and only 44 to Brucellergen (26.9 per cent)*

Similar discrepancies have been noted by the author. In 48 patients referred because of the suspicion of brucellosis, Brucellergen and heat-killed *Brucella abortus* bacterin were used simultaneously in opposite arms. Reactions to Brucellergen were read in twenty-four and forty-eight hours and to heat-killed vaccine in four to eight days There were 35 reactors to heat-killed *Brucella abortus* organisms (72 9 per cent) and 17 reactors to Brucellergen (35 4 per cent)

Among these patients with a negative reaction to Brucellergen and a positive reaction to heat-killed Brucella abortus *vaccine was one patient whose agglutination reaction had been positive in high titer (1·1280) prior to skin tests and whose blood culture yielded* Brucella suis (p 441). Another patient with negative Brucellergen and positive heat-killed *Brucella* vaccine skin tests had a positive agglutination reaction in a titer of 1:80 prior to skin tests and a positive stool culture for *Brucella.*

Particularly noticeable was the negative cutaneous reaction to Brucellergen in the presence of weakly positive reactions to heat-killed *Brucella abortus* organisms This occurred in 17 of the 48 patients. The diagnostic significance of weakly positive cutaneous reactions is the same as that of more definite reactions, indicating only a lesser degree of sensitization

Nonspecific cutaneous reactions to killed *Brucella* organisms is an unlikely explanation of the discrepancies described

[illegible]

in only 6 2 per cent of 96 persons in whom the agglutination reaction was positive in 55 1 per cent, the opsonocytophagic reac-

a negative reaction by others. There is no uniformity of opinion as to what constitutes a positive reaction. Many physicians still use the skin test as the sole diagnostic procedure.

Heat-killed Brucella abortus *vaccine* (bacterin) has been used in several thousands of persons over a period of fifteen years, employing 0.1 cc. of a stock suspension containing 2,000 million organisms per cc., except when hypersensitivity is expected, or special contraindications exist (p. 347). The test is done in the course of clinical and laboratory study *but is always deferred until agglutinin and phagocytic studies have been made.* The risk of producing occasional *skin necrosis* has seemed justified in view of the apparently greater sensitivity of this antigen (p. 333). To this regime may be added other antigens, such as the bacterial antigen complexes, used concurrently (pp. 334–337, 350).

Mixed strains of heat- or chemically killed Brucella *organisms* when used as skin-testing antigens are likely to produce *more* violent reactions than the *abortus* strain alone. There seems no advantage in their use since killed *abortus* organisms apparently are effective antigens in the presence of infection caused by any of the three species.

"Detoxified" Brucella *vaccine* (made from mixed *suis* and *abortus* strains treated with nitrous acid after the method of O'Neil [520] and Foshay [526]) is not suitable for skin testing. Moss [499] described use of a standard skin-testing dose of 0.05 cc. of a mixture of equal numbers of *Brucella abortus* and *suis* of a density equal to that of the turbidity of 50 p.p.m. of the U.S.P.H.S. fuller's-earth standard, producing reactions similar to that of other vaccines, with systemic manifestations and skin necrosis in the hypersensitive patients.

Brucellergen, a protein nucleate fraction of smooth *Brucella* organisms of any of the three species, was developed by Huddleson. "Data collected on more than 20,000 individuals who were either normal or actively infected show that it is a highly satisfactory and specific agent for detecting *Brucella* allergy," Huddleson stated. The author has found it unreliable.

The lesser sensitivity of Brucellergen as a skin-testing agent

antigenic properties,"[340] which occur in the production of vaccine due to use of heat or chemicals.

Early observations tended to show that patients reacting to one species of killed whole organisms reacted about equally to all three, whereas a species-specific reaction occurred in some patients using the fractions (B A C.) Later observations did not show uniform species-specificity of the B A C preparations. In patients previously skin tested or treated with any *Brucella* antigens more variable results were noted, suggesting that some had been desensitized whereas others may have been sensitized. (The work of Leon and Sosa [415] suggested that skin testing with *Brucella* antigens may cause skin sensitization developing in about one month, making it necessary to conclude skin testing within the space of two or three weeks in order to avoid false positive reactions.)

Reactions to *Brucella* B A C are read within thirty minutes and at twenty-four hours The immediate skin reaction is attributed to reaction of the preformed antibodies already present, the delayed reaction is ascribed to reaction of the antigen with tissue to form a reagent to which the tissue is hypersensitive [339]

No definitive conclusions could be drawn as to species-specificity of these skin tests, for various reasons Cultures were positive in only 6 of these patients and in 2 of the 6 the species had not been determined In the 4 patients in whom the species of *Brucella* was known, 1 was *abortus*, 1 *suis*, 1 *melitensis*, and in the fourth patient the organism was only identifiable as *suis* or *abortus* In the patient from whom *Brucella suis* was isolated skin reactions to *Brucella* B A C preparations could not be interpreted because of marked skin allergy to any substance including the saline control In the patient from whom *Brucella melitensis* was isolated there was no homologous skin reaction, however, this patient may have developed heterologous skin sensitivity from previous *Brucella* skin tests and treatment [415] In the patient from whom *Brucella abortus* was cultured, the immediate skin reaction was to the homologous B A C but he also had had prior treatment with *Brucella* vaccine In the patient whose strain could be identified only as *abortus* or *suis*, the skin reaction was greatest to B A C *melitensis*, this patient had had no prior skin tests or treatment

In the remaining patients skin sensitivity to *Brucella* B A C preparations was useful as a guide to selection of the antigen for desensitiza-

tion gave "positive" results in 72 9 per cent. These findings also strongly suggest the relative insensitivity of Brucellergen as a skin-testing antigen. It is well known however that skin tests performed with any antigen may be negative in a small percentage of *Brucella* infections, proved by culture.

Antiserum as a skin-testing agent was described by Foshay[232] in 1935, and used by Calder, Steen, and Baker[104] in their studies reported in 1939. The advantage lay in reading the reaction within thirty minutes However, several years later Foshay[238] stated that antibody skin testing had proved unreliable. In 100 patients with verified diagnoses antibody tests were positive in only about 50 per cent, with a higher proportion of failures in the acute phase than in the chronic stage of the disease.

Attempts were made by Leon and Sosa[435] to distinguish between *abortus* and *melitensis* infections by means of selective skin tests, using saline suspensions of formalin-killed *Brucella abortus* and *Brucella melitensis* separately, in concentrations of 100,000 cells per cc , 1,000,000 cells per cc , 10,000,000 cells per cc , and 100,000,000 cells per cc in 0.1-cc. amounts They found that the distinction could be made between *melitensis* and *abortus* infections The reaction was stronger with the homologous antigen *Brucella suis* was not included in these comparative tests. These infections were all culturally proved to be *Brucella*, of known species

An attempt was made by the author to distinguish between the infecting species of *Brucella* through intradermal tests with bacterial antigen complexes (B A C , Hoffmann)[340] made from each of the three separate species in a group of 134 patients referred with the *suspicion* of chronic brucellosis

The method of preparation of these bacterial antigen complexes of *Brucella* is based on the coprecipitation of proteins and toxins of *Brucella* filtrates by mild organic acids such as benzoic or salicylic and permits the separation of the combined toxins and proteins as a dry powder by dissolving away the organic acids with acetone or alcohol It is thought that this method of production "prevents and reduces denaturization, deterioration and subsequent loss of valuable

been no previous skin tests or therapeutic use of any *Brucella* antigen.

It may be ultimately shown that all three species of *Brucella* are so closely related antigenically as to preclude their use in skin testing for positive identification of the infecting species. However, when a discrepancy is noted it could be assignable to infection with more than one species, with skin allergy to only one having developed.

A few patients showed no skin allergy to any of the Brucella *B A C but gave definitely positive reactions to heat-killed* Brucella abortus *organisms.* It is therefore essential to use the *Brucella* B A C. only as an adjunct to heat-killed organisms in skin testing. In no instance have heat-killed *Brucella abortus* organisms given negative reactions in the presence of significant skin reactions to other skin-testing antigens used simultaneously (Brucellergen, *Brucella* B.A.C. of all three species, formalin-killed whole organisms of all three species). This suggests that heat-killed *Brucella abortus* organisms serve as an effective antigen to determine generic allergy, which assumption is further borne out by the fact that reactions to heat-killed *Brucella abortus* organisms were positive in all patients with positive cultures, regardless of the species of *Brucella* isolated.

Significance and Specificity

The significance of the intradermal reaction is, in general, comparable to that of the intradermal tuberculin test. A positive reaction, with exceptions to be noted, indicates that the patient has been infected with *Brucella.* The present status of the infection is still to be determined. A positive skin test in childhood has greater significance in suggesting recent and therefore probably active infection than in older age groups

It has been said [351] that a positive skin reaction does not have specific significance as a diagnostic measure unless the opsonocytophagic test demonstrates the presence of opsonins for the organism. The author has noted no such definite correlation between positive skin test and a "positive" opsonocytophagic test Absence of phagocytosis in all cells may be found in the presence of active or latent infection In fact, it is the lack of phagocytic activity that often seems to be so largely implicated in the continuation of symptoms Illustrative is the case referred to on page

tion and immunization but some paradoxical results were noted Some patients with marked skin allergy to one species of *Brucella* B.A.C responded better to treatment with one of the other species of *Brucella* B.A.C. although the majority responded clinically and serologically to the homologous antigen.

In one patient, a 49-year-old physician, there was a history of probable acute brucellosis following ingestion of raw cow's milk in 1938, and a second acute illness, also probably brucellosis, following ingestion of raw goat's milk in 1944 Cultures failed to yield *Brucella*. His skin reactions to both B.A.C. *abortus* and *melitensis* were marked (4+) and to B.A.C. *suis* slight (1+). Clinically and serologically he responded well to treatment doses of either B.A.C. *abortus* or *melitensis* and made a virtually complete recovery under continued treatment with a mixture of both.

In another patient, a 30-year-old female physician with a history of nine years of illness due to chronic brucellosis, immediate skin reaction to B.A.C. *abortus* was 1+ and to B A C. *suis* and *melitensis* negative Within twenty minutes after the skin inoculations she complained of stiffness and aching of the metacarpophalangeal joint of the right thumb, this was followed by malaise, backache, lymphadenopathy, and arthralgia the next day and then marked improvement. The delayed reaction to B.A.C. *abortus* was 4+, to *suis* 3+ and to *melitensis* 1+ B.A C. *melitensis* alone was given intradermally as a therapeutic test, producing a 2+ immediate reaction but with no focal or systemic reaction Six days later B A.C *abortus* alone was given, the immediate allergic reaction was 4+ and, within a half-hour, there was marked focal reaction with visible swelling of the metacarpophalangeal joint of the right thumb and of the right elbow joint. This was followed by a marked systemic reaction Then, following further dosage with B A C *abortus* in a 1 1000 dilution, there was a very satisfactory phagocytic and clinical response. Six months later she reported that *Brucella* of undetermined species was isolated from the stool.

Although this work using *Brucella* B A C. has not confirmed the observations of Leon and Sosa [455] as to species-specificity of skin testing, it suggests that the tests have some usefulness when the information is correlated with the clinical history and therapeutic response Further observations are necessary in a larger series of culturally proved cases in which the species of *Brucella* is identifiable and in whom there has

been no previous skin tests or therapeutic use of any *Brucella* antigen

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441: *Brucella suis* was isolated from the blood; Brucellergen skin test was negative; heat-killed *Brucella abortus* skin reaction was positive; blood-agglutination reaction had been positive two weeks previously in a 1:1280 dilution and was still positive in a 1:640 dilution; the opsonocytophagic test showed marked phagocytosis in 0 cells, moderate in 0 cells, slight in 17 cells, and none in 8 cells, a numerical index of 17. Similar low or "negative" phagocytic indices in the presence of positive or negative skin tests and in the presence of positive cultures have been encountered repeatedly. However, the evidence of present infection presented by a positive skin test is supported by phagocytic activity of the white cells and by agglutinins when present (p 252).

It has also been said [251] that the intradermal test should be considered nonspecific if positive in the presence of a negative agglutination and "negative" opsonocytophagic reaction. Such a combination of findings is not unusual in the presence of positive culture and has no significance beyond indicating a lack of immunologic response to past or present infection. In the presence of symptoms suggesting brucellosis, the triad mentioned may have quite the opposite significance attributed to it.

False Positive Reactions

Dermographia may result in immediate false positive skin reactions with any antigen. Use of physiologic saline as a control skin test, always advisable in any event, will serve to avoid such errors.

Previous skin testing or therapeutic doses of Brucella antigens presumably may result in skin sensitivity in uninfected persons. It is therefore essential to make careful inquiry into history of skin testing and or treatment and to interpret the skin reactions cautiously if such a history is elicited or suspected

Foshay [254] stated that any skin-testing agent may cause nonspecific or false reaction and that all require experience and judgment for correct interpretation

In view of the wide exposure to *Brucella* infection and the impossibility of excluding a past or quiescent or very mild active infection in any individual, a positive skin reaction cannot be used

as evidence of *Brucella* infection without clinical and other laboratory evidence. Whether or not it is ever positive in persons who have never been infected is impossible of demonstration.

False Negative Reactions

In infants there may be a lessened ability to produce antibodies, resulting in a larger percentage of negative skin reactions than in older children and adults. Also it is apparent that the younger the infant the shorter time has there been for antibodies to form.

In old age there may be lessened ability of the skin to react, perhaps due to senile changes in the skin itself and perhaps also to lessened antibody formation.

The "disimmune state" (*Kahn*) may follow a previous injection of an antigen which neutralizes all of the antibodies that can be mobilized at the time. An active massive infection is also thought to be responsible in some instances.

Skin changes such as edema, dehydration, and hyperemia due to fever, sunlight, or ultraviolet rays have been thought by various observers to cause false negative reactions.

Desensitization as the result of treatment occasionally may result in negative skin reactions in actively ill persons. (Benning[52] stated that when the skin test becomes negative in the course of treatment it denotes cure. This view is not concurred in by the author and by other observers,[-38] although such a state of desensitization usually is accompanied by improvement.)

A negative reaction may occur in the presence of positive culture, and therefore cannot be used to rule out brucellosis. However, a negative skin reaction, in itself, carries greater weight than does a negative agglutination reaction, if performed with a sensitive antigen.

Using heat-killed *Brucella abortus* vaccine as the skin-testing agent the author has encountered negative skin reactions in only about 5 per cent of persons having sufficient other laboratory and clinical evidence of brucellosis to allow a presumptive diagnosis.

That skin tests may be negative in the presence of active infection is shown by such findings as the following: In a case of

Brucella meningitis in a 7-year-old child,[641] *Brucella* was isolated from the spinal fluid but skin test was negative. In a case of *Brucella* endocarditis,[616] blood-agglutination reaction was positive in a 1:2560 dilution, *Brucella abortus* was recovered from the aortic vegetations and from spleen, kidney, heart blood, and lung at autopsy; intradermal reaction had been negative during life. In a case of *Brucella* infection with endocarditis, nephritis, and death from rupture of a mycotic aneurysm,[167] the blood-agglutination reaction was positive and *Brucella* was isolated from the blood stream; the cutaneous reaction was negative.

Reports of large percentages of negative skin reactions must be viewed with skepticism unless it is known what skin-testing antigen and criterion of negativity was used, i.e., whether all reactions less than strong were recorded as negative.

It is not known just how soon after infection skin sensitivity to *Brucella* develops. It is likely that it is a matter of three or more weeks. Skin tests would seem almost certain to be negative early in a recently acquired acute infection and should be withheld in any event, pending other laboratory study. The greater value of the intradermal test is in the chronic illness.

Morales-Otero and Gonzalez[497] stated that the cutaneous reaction should be considered only as evidence of hypersensitiveness in persons who had been in close contact with infected material, rather than as evidence of past or present infection. They found that 29 6 per cent of 212 milkers and cattle handlers gave positive intradermal reactions. Endemic abortion existed in the cattle in that region On a similar theoretic basis Huddleson[351] expressed the conviction that many cases of *Brucella* allergy are mistaken for chronic brucellosis He felt that those who come in contact with *Brucella* organisms may develop agglutinins or skin sensitivity to *Brucella* protein, with no history of having had clinical brucellosis. Lack of definite history of febrile illness or other evidence of active brucellosis cannot be used to disprove mild undiagnosed infection or latent infection. It is therefore impossible to determine what percentage, if any, developed hypersensitiveness without having acquired the infection itself.

Effect on Agglutinins

Routine or purposeful skin testing of individuals or groups, prior to performance of the other serologic studies, is to be decried because of the possible stimulation of agglutinins and opsonins and perhaps of complement, whet [illegible] skin-testing antigen consists of killed whole o [illegible] n, [illegible] fract [illegible] culture

and 1 *Brucella* vaccine. Agglutinins in titers of 1:80 persisted to the 4th week in 1 of the Brucellergen group and in none of the vaccine-tested group. (In 2 patients, not included in the above group, with acute febrile illnesses, one with a positive and the other with a negative intradermal reaction, agglutinins in titers of 1:320 developed two weeks following the skin tests.)

They considered that their study showed (a) that only titers above 1:80 can be regarded as due to contact with *Brucella* other than that of the skin test, (b) that "since only titers above 1:80 are usually regarded as indicative of active infection, the effect of the skin test can be disregarded entirely," (c) that excessive rise in agglutinins in patients with fever can be assigned to the fever itself. It was concluded that "except when high fevers are present, the agglutinin response to *Brucella* skin tests need not cause confusion in the interpretation of the agglutination tests."

Many factors were apparently not considered in interpreting results and in drawing tentative conclusions: (1) Others have found titers ranging up to 1:320 or higher following skin testing [151, 475, 714] (2) It is not the generally accepted view that "only titers above 1:80 are usually regarded as indicative of active infection." Titers of 1:80 or above are considered significant by the majority of observers (3) It has not been demonstrated that high fevers per se are productive of high agglutinin titers in uninfected persons (p 284). (4) Agglutination reactions were not carried out in dilutions above 1·160, ignoring the possibility of prozone reaction (p 293). (5) The group of 50 persons, of whom 36 per cent had positive intracutaneous reactions, were assumed to be free of *Brucella* infection because they were free of immediate or remote symptoms of brucellosis, this assumption ignores the fact that *Brucella* infection may be latent or subclinical (p. 67).

Agglutinins existing in low titer prior to skin testing often are stimulated to appear in higher titer following skin tests than in persons with no agglutinins prior to skin testing

Criscuolo [151] made observations on the curve of agglutinins on

the fourth, eighth, thirtieth, and sixtieth days following intradermal test with 0.1 cc. of heat-killed *Brucella* organisms. In the skin-test–positive group he found that agglutinins appeared in dilutions of 1:500 on the eighth day and disappeared in sixty to ninety days in some, in others agglutinins in titers of 1:500 appeared by the eighth day and were still present in titers of 1:80 or 1:100 on the sixtieth day, in another group agglutinins appeared by the fourth day in titers of 1:500 and had disappeared in sixty to ninety days, in a fourth group agglutinins appeared by the eighth day in only a 1:80 dilution, disappearing in sixty to ninety days; in a fifth group agglutinins in a 1:80 dilution appeared on the eighth day and were higher on the thirtieth day, in a sixth group agglutinins did not appear at any time following skin test. In a group of patients with negative reactions to the intradermal test he found that agglutinins appeared in a 1:80 dilution by the eighth day and disappeared by the thirtieth day in some, in others agglutinins appeared in titers of 1:500 by the eighth day and disappeared by the sixtieth day, in a third group no agglutinins appeared at any time

The inference is clear *The effect of skin testing, with positive or negative results, is unpredictable so far as titer or duration of agglutinins are concerned*

Effect on Opsonins

Intradermal tests for brucellosis may have a marked stimulating effect on phagocytosis within six days A low or "negative" phagocytic index may be transformed into a high or "positive" reaction by any effective skin-testing agent In 14 patients with very low indices on the day that skin test was performed, very high indices were found when the test was repeated six or more days later The skin test should neither precede the opsonocytophagic test nor the agglutination test [714]

Classification

A violent cutaneous reaction often is described as the only criterion of positivity It seems better to grade the reactions as

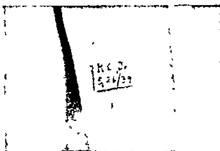
and 1 *Brucella* vaccine. Agglutinins in titers of 1:80 persisted to the 4th week in 1 of the Brucellergen group and in none of the vaccine-tested group. (In 2 patients, not included in the above group, with acute febrile illnesses, one with a positive and the other with a negative intradermal reaction, agglutinins in titers of 1:320 developed two weeks following the skin tests.)

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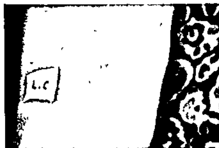
A



B



C



D



E



F

Fig 40 A Positive skin test, mild reaction, four days after intradermal vaccine
B Positive skin test in negress, moderate reaction, five days after intradermal vaccine
C Positive skin test, violent diffuse reaction four days after intradermal vaccine
D Positive skin test, violent localizing reaction, eleven days after intradermal vaccine
E Positive skin test, slough following violent reaction, two months after intradermal vaccine
F Positive skin test on arm, marked diffuse reaction, showing similarity to lesions on legs (same patient as in Fig 36 D)

weakly positive (+), positive (++), strongly positive (+++), and violently positive (++++) rather than to ignore the evidence to be gained by noting the degree of sensitivity shown. In most patients skin sensitivity is commensurate with tissue sensitivity in general. All have the same broad significance, i e, that at some time the patient has been sensitized to *Brucella*, presumably through actual infection, even though subclinical The term "*weakly positive reaction*" may be defined to designate a reddened, indurated area of about 5 mm. on the fourth to the eighth day. A "*positive reaction*" may be defined as one with redness and induration of more than 5 mm., perhaps surrounded by a mild erythema A "*strongly positive*" reaction may be defined as one with redness and marked induration greater than 10 mm, with erythema surrounding it. The term "*violently positive*" may be used to designate one that is accompanied by a markedly swollen and indurated area, with an angry erythema, often with lymphangitis, axillary adenitis, systemic reaction, and occasionally with central necrosis. Various degrees of skin reaction are illustrated in Figure 40

There are, occasionally, equivocal skin reactions which can neither be dismissed as negative nor recorded as positive but which should be kept under observation pending further study. Persistence of such a reaction for two weeks or more or increase in its prominence may result in reclassification as positive. Favorite and Culp [210] pointed out that a positive reaction tended to persist for several weeks whereas the negative reaction usually disappeared at the end of five days, certainly at the end of the first week.

Delayed Reactions

The author [208, 302] described delayed reactions to intradermal tests in 1934 An increasing number of persons have been observed in whom the intradermal reaction to heat-killed *Brucella* organisms was negative or equivocal at the end of four days but who showed a reaction with palpable, visible, reddened papule-formation of 5 mm. or more on the fifth, sixth, or seventh

day Recognition of these reactions may be of special importance in the presence of negative or low-titer blood-agglutination reaction, or in the presence of noninformative phagocytic indices and other clinical and laboratory data In several such instances therapeutic trial of *Brucella* vaccine was instrumental in establishing a diagnosis of brucellosis. Hagebusch and Frei [285] confirmed these observations in their extensive series of *Brucella* infections in childhood. They noted skin reactions developing as long as ten days after performance of the test. Criscuolo [151] reported observations of intradermal reactions on the fourth and eighth days in 337 persons using 0.1 cc of heat-killed *Brucella* organisms. In 44 2 per cent the reaction was greater on the fourth than on the eighth day In 22 2 per cent the reaction was more extensive on the eighth day than on the fourth day. *In 18 4 per cent the reaction was negative on the fourth day, becoming positive by the eighth day.* In 15 2 per cent a positive reaction was noted on the fourth day, disappearing by the eighth day

Skin Allergy Following Recovery

The status of skin sensitivity to intradermal *Brucella* antigens following apparent recovery has been the subject of controversy. Desensitization, as evidenced by negative skin reactions in treated patients, is not synonymous with recovery or cure, although sensitization to *Brucella* antigens usually lessens as improvement occurs [488, 542] Foshay [233] expressed the following opinion. "I do not believe one can judge anything useful about the progress of the average person by the results of any skin test This situation is much the same as it is in tularemia and in tuberculosis and possibly a few other infections, after recovery some patients maintain a high degree of sensitivity for the rest of their lives, others maintain a certain degree for from five to ten years and then lose it entirely and a small but unknown proportion lose all skin sensitivity very soon after convalescence is completed"

Skin Testing in Hypersensitive Patients

Foshay [234] warned that individuals who have recovered should be tested only with highly diluted materials, pointing to an in-

of killed *Brucella* organisms. Although the mixed-strain vaccines are known to produce a greater percentage of skin necrosis than does the *abortus* strain alone, the possible factor of strain and species variation of the original infecting organisms cannot be dismissed The geographic origin of the patient seems of little help in evaluating this factor since the population of the United States shifts so rapidly.

Definite contraindications to use of stock dilutions of *Brucella abortus* vaccine, mixed vaccines, or culture filtrates seem to be ocular or nervous-system manifestations suspected to be due to *Brucella* allergy or infection It is conceivable that irreversible focal changes might be induced in hypersensitive patients. In patients giving histories of contact with cattle or their products of conception or animal carcasses or of laboratory exposure, caution may be exercised by employment of a 1:10 or 1:100 dilution of the skin-testing antigen in amounts of from 0 02 cc to 0 05 cc. If negative on the eighth day the skin test may be repeated using the usual concentration of antigen, probably without risking sensitization from the initial skin test This regimen may be used routinely if time permits

Through failure to observe this precaution in a young woman, not suspected of having had contact with cattle, an area of necrosis about 3 × 3 cm. was produced. It was then learned that she had shared in the general care of cattle on her country estate However, in this, as in most instances of skin necrosis among the author's patients, there was excellent clinical and serologic response following the initial sharp, febrile, systemic reaction Although the patient has remained hypersensitive, as shown by sharp reactions following three separate attempts to bring about desensitization through two intramuscular doses of *Brucella abortus* bacterin in a 1·10,000 dilution and one of Castaneda's M B P in a similar dilution, the early, frequently relapsing febrile attacks ceased

In only 3 other patients was a state of hypersensitivity apparently induced or aggravated by skin testing with heat-killed *Brucella* vaccine, with failure of desensitization even by dilutions as

stance in which the disease, quiescent for six years, was reactivated by a skin test, with resultant disability for almost a year.

Any antigen may provoke a severe reaction with local necrosis Brucellergen is considered the agent least likely to produce skin necrosis. Reports on its reaction vary considerably, however. Angle and his coworkers [23] reported no skin necrosis from Brucellergen among 168 persons simultaneously skin tested with Brucellergen and heat-killed *Brucella* vaccine, whereas 9 patients showed necrosis at the site of the intradermal inoculation with the heat-killed vaccine. On the other hand, Menefee and Poston [475] skin tested 1,122 students with Brucellergen, noting positive reactions in 127 of them; 43 had severe local reactions with lymphadenitis. Of these, 22 had axillary adenitis, 24 had marked febrile systemic reactions, and 5 had fever of 104 or higher and required hospitalization for three or four days. One had a slough 6 × 4 cm., healing in nine weeks. Griggs [278] reported skin necrosis from Brucellergen in 11 instances and near necrosis in 14 other patients. The author has seen several sloughs from Brucellergen

The marked variation in severity of skin reactions as well as of response to treatment doses produced by any single antigen is noteworthy. Variations in technics or amounts of skin-testing agents are apparently not the factor, since standardized amounts are used by most workers Lack of standardization of the skin-testing agents has to be considered as a possible factor (e g., Brucellergen may be prepared from any of the three species of *Brucella*) Variation in skin sensitivity caused by various subspecies of *Brucella* in different localities may be an important factor Syringes contaminated with other antigens must also be considered (p 348)

Skin necrosis occurred in about 3 per cent of the positive reactions among approximately 600 of the author's patients from all sections of the United States and many parts of the world, using a standardized amount of 0 1 cc of heat-killed *Brucella abortus* vaccine However, it has been notable that a relatively large number of patients referred after skin testing elsewhere have exhibited scars of skin necrosis, usually following mixed strains

of killed *Brucella* organisms. Although the mixed-strain vaccines are known to produce a greater percentage of skin necrosis than does the *abortus* strain alone, the possible factor of strain and species variation of the original infecting organisms cannot be dismissed. The geographic origin of the patient seems of little help in evaluating this factor since the population of the United States shifts so rapidly.

Definite contraindications to use of stock dilutions of *Brucella abortus* vaccine, mixed vaccines, or culture filtrates seem to be ocular or nervous-system manifestations suspected to be due to *Brucella* allergy or infection It is conceivable that irreversible focal changes might be induced in hypersensitive patients In patients giving histories of contact with cattle or their products of conception or animal carcasses or of laboratory exposure, caution may be exercised by employment of a 1:10 or 1:100 dilution of the skin-testing antigen in amounts of from 0 02 cc to 0 05 cc If negative on the eighth day the skin test may be repeated using the usual concentration of antigen, probably without risking sensitization from the initial skin test. This regimen may be used routinely if time permits

Through failure to observe this precaution in a young woman, not suspected of having had contact with cattle, an area of necrosis about 3 × 3 cm. was produced It was then learned that she had shared in the general care of cattle on her country estate However, in this, as in most instances of skin necrosis among the author's patients, there was excellent clinical and serologic response following the initial sharp, febrile, systemic reaction Although the patient has remained hypersensitive, as shown by sharp reactions following three separate attempts to bring about desensitization through two intramuscular doses of *Brucella abortus* bacterin in a 1 10,000 dilution and one of Castaneda's M B P. in a similar dilution, the early, frequently relapsing febrile attacks ceased

In *only 3 other patients was a state of hypersensitivity* apparently induced or aggravated by skin testing with heat-killed *Brucella* vaccine, with failure of desensitization even by dilutions as

great as 1:100,000 of the stock suspension containing 2 billion organisms per cc. In 16 other patients in whom skin necrosis occurred, there was no special difficulty in bringing about desensitization through use of vaccine in dilutions of 1:10,000 or less, providing the necrotic skin area was allowed to heal before treatment was begun.

In 21 patients who had either very strongly reacting or necrotizing skin reactions, no further vaccine was needed to bring about complete clinical recovery, lasting from ten months to more than five years (pp. 171–465).

Griggs [278] encountered serious difficulty in large numbers of hypersensitive patients. In further skin testing he found that Brucellergen had to be diluted from the 1:12,000 dilution supplied *to 1:120,000 to avoid necrosis* and that his attempts at desensitization with heat-killed or oxidized *Brucella* vaccine required dilutions of extreme degree.*

Technic

Use of tuberculin syringes, preferably of 0 5-cc capacity, is recommended so that the very small doses (0 02 to 0 1 cc) may be measured accurately. Short, fine-gauge needles, with short bevel, are desirable to allow of easy access to the very superficial layers of the epidermis, without likelihood of producing hemorrhage into the epidermis through trauma

Cleansing and Sterilization of Syringes and Needles

Meticulous cleansing, prior to sterilization of needles and syringes that have been used for *Brucella* antigens or other antigens, is essential to avoid injecting contaminating substances intradermally Syringes once used for skin testing with old tuberculin and then used for other skin-testing agents may give false reactions, in tuberculin-sensitive patients, to the tuberculin which so tenaciously adheres to syringe barrels and plungers, in spite of ordinary cleansing and boiling Supposedly great dilutions of *Brucella* antigens actually may be far less dilute because of the same

* Aureomycin or chloromycetin may bring about desensitization, allowing subsequent use of *Brucella* antigens (See Addenda, p 538)

tendency of *Brucella* antigens to adhere to syringes (and perhaps to vaccine bottle stoppers), giving rise to unexpectedly severe reactions.

One physician noted definite reactions in some hypersensitive patients even to dilutions of *Brucella* antigen as great as 10^{-450}! Realizing that the *Brucella* molecule must disappear long before such a fantastic dilution is reached he discarded all antigens and glassware then in use Using fresh antigens and syringes he then found that in no patient did reaction occur to dilutions beyond the eighteenth power.

Syringes once used for tuberculin injections should not be used subsequently for *Brucella* antigens Syringes used for *Brucella* antigens should be soaked overnight after each use in a sulfuric acid dichromate solution, then washed with soap and water, thoroughly rinsed, and autoclaved. If sterilization by boiling is the method employed, a separate small sterilizer for each type of skin-testing antigen is a worthwhile added precaution, to prevent contamination of the syringes from various antigens which may adhere to the sterilizer. This would be particularly important if the separate species of *Brucella* were being employed as killed organisms or bacterial antigen complexes, or if comparisons were being made between different types of antigen, such as Brucellergen and killed organisms. It is possible that some reports which describe skin reactions to Brucellergen as occurring as frequently and in the same degree as those to killed *Brucella* organisms may be based on unwitting mixture of antigens through such contamination.

Control tests with sterile physiologic saline are recommended

Heat-Killed Brucella *Organisms*

Under ordinary circumstances undiluted heat-killed *Brucella abortus* bacterin (2 billion organisms per cc) is injected intradermally in the very superficial layers of the skin The amount may be from 0 05 cc to 0 1 cc The reaction is read at the end of four days and, if negative, again at the end of seven or eight days It is evaluated and recorded in accordance with the criteria previously discussed

Other *Brucella* vaccines are used and reactions read in a similar manner. The immediate or delayed allergic (urticarial) reactions ordinarily are considered of no special significance.

Recent experience indicates the accuracy of tests made with amounts as small as 0.02 to 0.05 cc. When multiple skin tests are done with different antigens these smaller doses are desirable in order to minimize systemic reaction (and perhaps sensitization).

When dilutions of 1:10 or greater are used and result in negative reactions, the test is repeated with the usual stock concentrations within a fourteen-day period.

Brucellergen

Brucellergen is used in amounts of 0.1 cc., intradermally. Huddleson stated that the reaction is characterized by a circumscribed erythema, edema, and induration, varying in diameter from 2 to 10 cm It is read at the end of twenty-four and forty-eight hours. As with heat-killed *Brucella* vaccine, the local reaction may be accompanied by intensification of existing symptoms

Bacterial Antigen Complexes

Bacterial antigen complexes (B.A.C., Hoffmann) of each separate species are injected in amounts of 0 02 cc. The immediate allergic reaction is read within thirty minutes and the possible delayed reaction in twenty-four hours If equal reactions to two or all three antigens result, repetition of the tests after four to seven days will usually result in clarification through lessening or disappearance of the reaction to the species of lesser importance Their use is still experimental

ADDITIONAL DIAGNOSTIC AIDS

Abnormalities of blood (p 178) were observed so consistently by Calder and his coworkers [111] as to appear to represent a fundamental part of the disease They stated that they are duplicated in their entirety in no other known disease The occurrence of such blood findings properly may influence diagnostic judgment in some measure in situations which are difficult to evaluate

Staub [449] reported leukopenia and relative lymphocytosis as invariable findings in 150 cases of brucellosis in the Northwestern United States Others, including the author, have noted no such uniformity. However, these deviations from the normal occur in the majority of cases and may have some confirmatory diagnostic value when found They may also appear in other infections, including some virus infections. They must be interpreted with caution and used only as supporting evidence

Blood-sedimentation rates also may furnish some confirmatory evidence of *Brucella* infection, particularly in the differential diagnosis between brucellosis and rheumatic fever or tuberculosis, when a normal or low rate is found A normal rate cannot be said to be characteristic of brucellosis, however, high rates occasionally occur, especially in the presence of joint involvement or other localized pathology

Reaction to the skin test often furnishes valuable additional evidence that may be sorely needed in evaluation of the patient whose other tests are not sufficiently informative Patients often complain of concurrent intensification of subjective or objective symptoms which had been under suspicion as possibly indicative of brucellosis If, immediately following subsidence of the cutaneous reaction, the patient feels markedly better, with lessening or disappearance of symptoms, particularly with a concomitant rise in the phagocytic index, this reaction may be considered significant. The patient's desire to produce evidence of brucellosis must be considered, in the presence of psychoneurosis

Brucella vaccine as a therapeutic test in doubtful cases has been discussed elsewhere The occurrence of a systemic reaction alone is not sufficient to prove the existence of active infection, for sensitivity may persist after recovery from an old infection (p 345) The most significant reactions in these doubtful cases are, coincident exacerbation of existing symptoms, followed closely by apparent improvement, or improvement in the absence of any systemic reaction to vaccine This evidence is strengthened by a coincidental rise in the opsonic index (Agglutinin response has no apparent significance.) Further supportive evidence is added

if subsequent recurrence of symptoms is accompanied by lessening of phagocytosis and improvement again is concomitant with reestablishment of a high phagocytic activity (p. 325).

Intradermal reactions resembling existing skin lesions are observed occasionally. In several patients with the rather distinctive pinkish-red or orange-red papular skin eruptions, the reactions to the intradermal test simulated the skin eruptions so exactly as to be almost indistinguishable from the lesions. Figure 40-F illustrates this similarity of a violently cutaneous reaction to lesions which resembled erythema nodosum. In other instances the intradermal reactions were only moderately active (p 138).

Summary of Diagnostic Data

An attempt is made below to sum up diagnostic data in patients never previously skin tested, *in the presence of clinical symptoms suggesting brucellosis.*

1. None of the three tests commonly used—the intradermal, agglutination, and opsonocytophagic reactions—individually is of sufficiently specific diagnostic importance, without supportive information from the other tests, history, and physical examination, to allow definitive diagnosis.
2. Any of them may produce significant reactions in asymptomatic cases, and any may be negative or noninformative in cases of active infection proved by culture of the organism. However, agglutinins in titers of 1 80 or above usually signify active *Brucella* infection. Lower titers are suggestive.
3. If the intracutaneous and agglutination reactions and culture all are negative, we do not know whether or not the patient ever has had brucellosis The opsonocytophagic test, which merely indicates the phagocytic activity of the blood toward *Brucella*, has little diagnostic significance alone However, presence of specific opsonins are unlikely except as the result of past or present infection.
4. If the intracutaneous test is positive we know that the patient has an old or recent infection, of undetermined activity If negative it has no definite significance.

5 If the positive intracutaneous test is accompanied by a low to moderate phagocytic index it is presumptive evidence that the patient has not recovered from the old infection.
6 If a positive intracutaneous test is accompanied by a high phagocytic index, such a reading may be referable to, (a) an undiscovered focus of infection, (b) an overwhelming infection, or (c) failure of desensitization
7 The tests must be used as a battery, including culture whenever possible.

Any criteria as to laboratory diagnosis of brucellosis must be expressed in general terms rather than as dicta. There are many exceptions and apparent contradictions. It is impossible to formulate absolute laboratory criteria that will evaluate every patient. In all probability, as many errors may be made in ruling out brucellosis in favor of a diagnosis of psychoneurosis or other illness as the converse

The overenthusiasm in making a diagnosis of brucellosis exhibited by some is often equalled by the zeal of others in ignoring the possibility It seems best to arrive at no more than a tentative diagnosis of brucellosis in the absence of cultural proof, until clinical response, supported by laboratory evidence, has been demonstrated It is also unwise to give a firm negative opinion on the basis of negative laboratory procedures

Differential Diagnosis

Brucellosis must be considered in the differential diagnosis of any obscure illness, acute or chronic, febrile or afebrile.

A full discussion of its differential diagnosis would constitute a system of medicine The more frequently encountered differential diagnostic problems and some conditions which have furnished special problems will be discussed.

Hughes [863] stated that malaria, tuberculosis, liver abscess, and

erroneous diagnoses were typhoid fever, influenza, and tuberculosis. Others were malaria, pyogenic septicemia, various respiratory infections including bronchitis, sinusitis, and pneumonia. Appendicitis and cholecystitis accounted for 7 per cent of the erroneous impressions. Diseases of the cardiovascular system were wrongly diagnosed, including subacute bacterial endocarditis, pericarditis, and hypertension, in a lesser number. Less frequent diagnoses were liver abscess, infantile paralysis, spastic colitis, carbon monoxide poisoning, tetanus, nervous breakdown, "liver trouble," and "eye trouble."

Taylor and his coworkers[601] reported correct diagnoses in only 38 per cent of 232 cases of brucellosis. The remaining 62 per cent had been erroneously diagnosed as grippe, bronchitis, pneumonia, pleurisy, pulmonary tuberculosis, typhoid or paratyphoid fever, articular rheumatism, malaria, angina, diphtheria, menopause, neurasthenia, or gallstones, or had been diagnosed as meningitis, orchitis, intercostal neuralgia, sciatica, or renal congestion, without realization of the etiologic factor.

McGinty and Gambrell[471] listed 38 diseases or syndromes from which brucellosis must be differentiated. Hartsock[314] considered this list "exaggerated but not far from the truth," adding that the disease must be considered in general terms, as one does tuberculosis and syphilis, and as affecting any part of the body.

Psychoneurosis is among the most common and difficult conditions to differentiate from chronic brucellosis. It is discussed at length on pages 244–246, 367–406

Ebaugh[187] stated that many conditions, including brucellosis, may be called psychoneurosis because the underlying condition is not diagnosed Persons with a psychoneurosis may have an independent organic disease and "a diagnosis of a psychoneurosis can only be made on positive findings such as infantilism and immaturity, regression and fixation, irrational fears, exaggerated behavior, exaggerated mood changes, obsessions, rituals, overestimation of self, disturbance in work capacity, use of time, money and food, clothes, useless repetitive behavior, senseless hostility, competitive envy and aggression with fear of retaliation" It has

long been a custom to make a diagnosis of psychoneurosis on the basis of lack of physical or manifest laboratory findings alone

Intravenous injection of sodium amytal as a test for latent anxiety was described by Susselman and Feldman.[653] They pointed out that anxiety or tension states may give rise to symptoms referable to many systems of the body, even in patients not considered to be psychoneurotic, and that symptoms due to organic disease may be exacerbated because of tension The test was suggested only to supplement thorough physical and psychiatric investigation.

Allan,[10] in attempting to distinguish between the weakness and fatigue due to physical illness and that of psychic origin, mentioned complaints of more than three years duration without any physical disorders to account for them, as pointing to psychogenic states. The diagnostic procedures used to rule out brucellosis among these patients consisted of only the blood-agglutination reaction. Brucellosis is one of the physical disorders which commonly does remain undiagnosed for three years or more, it is a matter of speculation as to how many of the 300 patients studied actually had chronic brucellosis Skin test, opsonocytophagic test, and culture were not employed

Tuberculosis of lungs, bone, and other tissues may be very difficult to distinguish from lesions caused by *Brucella.*[47, 113, 525, 609, 655] The blood-complement–fixation reaction for tuberculosis may be of value under some circumstances. Its status is controversial and its availability is not general. Occasionally blood-complement–fixation reactions for tuberculosis will occur in patients in whom no other laboratory, clinical, or radiographic evidence of tuberculosis can be found after prolonged observation, apparently as a cross-reaction to *Brucella* or other infections

Coexistence of brucellosis and pulmonary tuberculosis could hardly be of great rarity because of the wide prevalence of both infections. Their actual coexistence has been demonstrated by the author in 4 patients and very probably overlooked in others Tuberculosis, anthrax, and brucellosis in 1 patient was reported by de la Cruz.[170]

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Coexistence of syphilis and brucellosis is, of course, not uncommon.

Sarcoidosis occasionally may be confused with brucellosis early in its course, clinically, because of eosinophilia, leukopenia, splenomegaly, hepatamegaly, and lymph-node involvement, and histologically because of the tubercle-like lesions which resemble both those of tuberculosis and brucellosis. The frequent alteration in plasma proteins, with marked increase in the globulin fraction, may be a distinguishing feature.

Rheumatic fever, in its atypical forms, is among the most difficult problems Even in the early stages of classical rheumatic fever, brucellosis may present an almost identical syndrome In the atypical rheumatic infection, without local redness or heat in joints, the diagnosis may not be apparent until the process is full-blown When rheumatic infection and chronic *Brucella* infection coexist, the distinction is usually impossible early in the disease. Since rheumatic fever was commonly encountered in naval service, it was not surprising that patients with brucellosis were erroneously diagnosed as having the former disease. However, on more than one occasion, the error of diagnosing the illness as brucellosis was made, later to find unmistakable evidence of rheumatic fever, with its complications and sequelae.

Jones [379] listed the following criteria as constituting reasonably certain diagnostic evidence of rheumatic fever. (1) any combination of the major manifestations (carditis, arthralgia, chorea, nodules, and a verified history of previous rheumatic fever), (2) the combination of at least one of the major manifestations with two of the minor manifestations (fever, abdominal or precordial pain, erythema marginatum, epistaxis, pulmonary changes, and laboratory abnormalities), (3) the presence of rheumatic heart disease increases the diagnostic significance of the minor manifestations, when no other cause for these manifestations exists.

In 1 of 2 such patients erroneously diagnosed by the author, abdominal pain was an outstanding manifestation. It was attributed to infected mesenteric lymph glands Later typical carditis developed This patient apparently had a chronic but unimpor-

Hyperthyroidism may need differentiation from chronic brucellosis because of the similarity in subjective symptoms (especially fatigue, tachycardia, and "nervousness") and in the dearth of physical findings. Coexistence of chronic brucellosis and hyperthyroidism is not rare. There may be a relationship, on a psychosomatic basis.

Arthritis (hypertrophic or atrophic) due to *Brucella* infection may be indistinguishable from that of other origin except as the result of therapeutic trial of *Brucella* vaccine. The problem is rendered particularly difficult because of the lack of specific laboratory or clinical proof of the etiologic factor in joint involvement in general Hardy [290] and others have mentioned the usual lack of detectable physical abnormality in arthritis due to brucellosis but this is not a constant differential point (p. 203). The diagnosis of brucellosis in a patient with arthritis obviously does not prove etiologic relationship, without clearly defined response to specific vaccine therapy. Brucellosis and unrelated arthritis may coexist. Isolation of *Brucella* from synovial fluid may be possible in some instances (p 214). Rheumatoid arthritis may be especially difficult of differentiation (p. 205).

Syphilis is considered as relatively easy of differentiation, in spite of the protean nature of both syphilis and brucellosis, because of blood and spinal-fluid reactions. However, a false positive Kahn and/or Wassermann reaction may occur in brucellosis. In 1 case the Kahn test was positive and Wassermann negative, ultimately, a diagnosis of brucellosis was established and the Kahn test returned to negative In another, both Kahn and Wassermann tests were positive, with no history or clinical evidence of syphilis (In this instance, however, congenital syphilis or a concealed history of syphilis could not be ruled out.) Schmidt [603] reported the occurrence of false positive Wassermann reactions in brucellosis Rennella [81] reported 8 patients who showed positive Kahn tests and 1 with positive Wassermann test, "all of them being cases of brucellosis" In 5 of the cases the test became negative. Later [504] 4 or 5 other similar cases came to his attention.

cedures and observation of inoculated guinea pigs, such earlier differential diagnostic criteria may be vital as a basis for treatment [313]

Tularemia usually may be distinguishable clinically and on the basis of blood-agglutination reactions If agglutination occurs both with *Brucella abortus* and with *B. tularense*, the higher titer usually is indicative of the active infectious agent. According to Pennell and Huddleson,[329] an additional differential-diagnostic method is furnished by skin testing with protein nucleate solutions of both organisms, they found no cross-sensitization.

Infectious mononucleosis usually may be distinguished by the blood picture and heterophile antibody reaction, along with clinical signs and symptoms, but the differential diagnosis may be difficult.[592] In 2 instances the most careful study did not result in differentiation between the two diseases for a period of several weeks, even then the diagnosis of mononucleosis was made largely on clinical evidence.

Menefee and Poston [475] quoted an instance in which brucellosis might readily have been diagnosed in a patient with fever and chills of four days duration Brucellergen skin tests were positive, *Brucella* agglutinins were present in a titer of 1:160, and the opsonic index was 37 White cells were 4,300 with relative lymphocytosis On the third hospital day he developed sore throat and slight generalized enlargement of lymph nodes White blood count rose to 18,000 with 26 per cent monocytes and heterophile antibody reaction was positive in a 1 1,024 dilution. (It must be assumed that the skin test did not precede the blood-agglutination test with *Brucella* and the opsonocytophagic test, and that actual *Brucella* infection did not precede the mononucleosis or coexist with it)

Whether or not the lymphocytes show pathognomonic changes in mononucleosis is debated [414] In the absence of agglutinins with sheep red cells, the blood picture and clinical manifestations may leave the diagnosis in doubt Gardner and Paul [247] found the heterophile antibody reaction was negative in 40 per cent of 86

tant *Brucella* infection as shown by an agglutination reaction in a low dilution, generalized lymphadenopathy, positive skin test, and the opsonocytophagic reaction. In the other patient, pulmonary changes, consisting of scattered areas of consolidation, occuring concomitantly with rapidly developing rheumatic heart disease, were the first definite evidences that the diagnosis of brucellosis did not acount for the patient's major illness. Whereas a normal erythrocyte sedimentation rate militates against the diagnosis of rheumatic fever, a high rate may be found in either disease (p. 180).

Endocarditis of rheumatic origin may be distinguishable from that of *Brucella* origin only by cultural methods. *Brucella* infection must be suspected in endocarditis whenever other etiology has not been proved However, the finding of *Brucella* septicemia does not prove that the endocardial lesions are not due to previously existing or concomitant rheumatic infection. Therapeutic response to penicillin and sulfadiazine may be the only evidence of subacute bacterial endocarditis. Response of an undiagnosed endocarditis to streptomycin and sulfadiazine may prove to be a differential procedure but is, as yet, unproved.

Meningitis (tuberculous, influenzal, acute luetic, and torula)[168, 268] must be differentiated by cultural study and animal inoculation *Encephalitis, myelitis,* or meningitis due to *Brucella* may be clinically identical with those seen in similar disease processes of other origin Nervous-system complications similar to those seen in undulant fever have been described with typhus, typhoid fever, and mumps. In *Brucella* meningitis there may be startling but evanescent central–nervous-system symptoms such as hemiplegia, paraplegia, asphasia, or diplopia. Onset usually is gradual and insidious, however The mononuclear pleocytosis is similar to that in syphilitic meningitis

A meningitis occurring in the course of proved or suspected undulant fever and showing a relatively high cerebrospinal fluid cell count, originally with a large proportion of mononuclear cells, should be considered as probably due to *Brucella* infection Since the organism may not be isolated until after lengthy cultural pro-

(Westergren) and eosinophilia of 15 per cent. Precipitin reaction for trichinosis was positive in a dilution of 1:1,280. Subsequent skin test with *trichinella* extract was positive The patient had forgotten an attack of gastroenteritis which had preceded the present symptoms by some weeks and which had been attributed by her family physician to an organism probably of the *Salmonella* group which had been causing epidemic dysentery in Cuba at the time.

Amebiasis may simulate chronic brucellosis, D'Antoni [159] pointed out. Amebae are likely to be overlooked unless multiple stools are expertly examined.

Shigellosis, also remarkably similar to brucellosis in some of its manifestations, requires special cultural technics.[159]

Eosinophilic leukemia may need differentiation from brucellosis in the instances of marked eosinophilia with relatively high white blood counts such as are uncommonly found in brucellosis (p 179). Bone-marrow study is the usual means of distinction.

Acute or chronic abdominal conditions, including cholecystitis and appendicitis, may be caused or simulated by *Brucella* infection (p. 181), with indistinguishable clinical findings In *cholecystitis,* isolation of *Brucella* from aspirated bile, with or without evidence of systemic *Brucella* infection, may be the only means of differentiation In the presence of hepatitis radiographic study of the gallbladder may be rendered valueless, whether due to brucellosis or other cause, because of poor concentration of the dye. In the presence of clinical evidence of *appendicitis,* lack of rectus muscle rigidity may be the only distinguishing feature between *Brucella* and other infection, since operation may not be deferred pending serologic and other study, culture of the excised tissue may be the only means of diagnosis (p 183) In the syndrome suggesting *perforation of an abdominal viscus,* lack of typical boardlike rigidity led to consideration of brucellosis as a possible cause in one patient (p 182)

Infectious hepatitis (virus jaundice) may closely resemble the similar syndrome occurring in brucellosis, particularly in the patient with slight or no icterus Liver-function tests are not

cases analysed. Definitive diagnosis in all cases of mononucleosis may have to await discovery of its etiology.

Acute infectious lymphocytosis usually may be differentiated by an extremely high lymphocyte count consisting of small lymphocytes, with total high white blood cell count and absence of splenomegaly and lymphadenopathy.[60]

Virus infections of unknown type, as well as many of the known forms, may produce clinical signs and symptoms such as fever, malaise, hepatitis, and splenitis, together with leukopenia and relative lymphocytosis, which may resemble brucellosis.

Histoplasmosis, because of fever, hypochromic anemia, hepatomegaly, splenomegaly, and lymphadenopathy, together with anorexia, loss of weight, and other symptoms, may cause confusion with brucellosis. Diagnosis is best established by histologic examination of biopsy material and smears or scrapings from superficial lesions The positive differential-diagnosis method is the identification of the characteristic morphology of the mycelial form of *Histoplasma capsulatum*.*

Trichinosis may enter into the differential diagnosis in the presence of eosinophilia, marked eosinophilia has been found in brucellosis (p. 179). Repeated blood-precipitation or complement-fixation tests for trichinosis may be necessary, in addition to muscle biopsy False reactions for trichinosis occasionally occur. It seems advisable to withhold performance of the allergic skin test with *trichinella* extract until there has been adequate opportunity for performance of repeated blood tests since the skin test for trichinosis may affect the blood reaction.

A 39-year-old woman living in Cuba was referred with a tentative diagnosis of brucellosis. She complained of lassitude, easy fatigability, anorexia, muscle soreness, and stiffness of the neck of five weeks duration, with low-grade fever. Physical examination was negative Laboratory studies were negative for *Brucella* infection, the only abnormalities found were a sedimentation rate of 35 mm in one hour

* A complement-fixation reaction has recently been described by Tennenberg and Howell and by Furculous, Bunnell, and Tennenberg (*Pub Health Rep* 63 163–168, 169–173, 1948)

Typhoid fever may not be distinguishable from brucellosis by the respective agglutination reactions alone. Agglutinins for typhoid organisms may be present in patients proved by culture to be suffering from *Brucella* infections and vice versa. However, if agglutinins against both organisms are present they are likely to be in higher titer against the actual infecting organism.[257] Isolation of *B. typhosus* or *Brucella* may be the only means of distinction.

Spotted fever (Rocky Mountain spotted fever, Eastern spotted fever) may need to be differentiated from brucellosis because of the clinical similarity of the illnesses prior to the appearance of the rather characteristic rash and because the blood-agglutination reaction with *Bacillus proteus OX 19* may occur in brucellosis as a cross-reaction.

Tsutsugamushi fever (scrub typhus, Japanese river fever, mite typhus, exanthematous glandular fever) may have clinical similarity to brucellosis because of headache, anorexia, fever, malaise, backache, muscle soreness, arthralgia, chills, frequency of urination, stiffness of neck, hyperesthesia, cough, fatigue, and tendency to bradycardia, which may be found in either illness. Paucity of physical findings also is common to both. Splenomegaly was present in 8 of the 25 cases seen by Greenfield.[274] Leukopenia in mild degree (4000 to 6000 cells) is likely to be present in both. Differential diagnosis depends upon a positive Weil-Felix reaction with *B. proteus OX-Kingsbury* and upon symptomatology and history of possible exposure. Necrotic ulcer at the site of the mite bite and regional lymphadenopathy are of diagnostic importance when present.

Haverhill fever may be confused with brucellosis, especially when no characteristic rash appears.[647] Isolation of *streptobacillus moniliformis* (*Haverhillia multiformis*) from blood or articular fluid is usually possible.

"*Q*" *fever* may be differentiated by agglutinins and complement fixation against *R. Burneti* usually in the second week of the disease. Lack of leukocytic response and some clinical similarity may cause confusion with brucellosis.[146, 271, 372, 608] History of con-

specific since hepatitis may occur in brucellosis. History of known exposure to infectious jaundice, of a definite attack from which recovery was incomplete, of inoculation with contaminated yellow fever vaccine, or of recent transfusion of blood or plasma and negative multiple tests for brucellosis may make the distinction

Hodgkin's disease, especially the Pel-Ebstein variety, may very closely resemble brucellosis (p. 132). Recovery of *Brucella* from lymph nodes of patients with Hodgkin's disease may pose a most difficult diagnostic problem. In one of the author's patients brucellosis coexisted with an ultimately fatal Pel-Ebstein type of Hodgkin's disease. Lymph-node biopsy early in the illness gave the histologic picture commonly seen in brucellosis rather than in Hodgkin's disease Lesions in spleen, liver, and lymph nodes at necropsy were inconclusive.

Diseases of the collagen system (lupus erythematosus dissemi- [illegible] nodosa) may be very difficult of differenti- [illegible] with negative physical and [illegible]

Endocrine dysfunction often presents difficult diagnostic problems (p 270). *Menopausal symptoms may be confused* with the vague symptoms of low-grade chronic brucellosis, weakness, nervousness, flushes, and vague abdominal, muscular, and joint aches and pains being common to both. When the conditions coexist there may be a particularly confusing situation which can be differentiated only by independent trial of endocrine therapy or specific vaccine therapy. *Brucella* infection or allergy may be the actual cause of endocrine dysfunction.

Malaria, in its acute form, may be difficult of differentiation unless parasites can be demonstrated

Chronic malaria occasionally may produce prolonged illness with slight to moderate anemia, slight icterus, and enlargement of the liver and or spleen, with low-grade or no fever [400] Although parasites are usually present in the circulating blood, their density may be very low Coexistence of *Brucella* and malaria has resulted in great confusion

and McNeil media will give growth to the organism despite negative blood or bone-marrow examination. There is usually a reversal of the albumin-globulin ratio with a rise in the globulin fraction beginning early in the disease and reaching as high as 8 Gm. per 100 cc.[389]

Bartonella infection (Carrion's disease, Oroya fever, Verruga peruana) may require differentiation from brucellosis, in the Oroya fever stage. Differential diagnosis depends upon demonstration of the *B. bacilliformis* in the blood or on culture of the organism from the blood.[700]

Filiariasis bancrofti, because of the usual localized nature of the symptoms, is not often a problem in differential diagnosis. Occasionally subjective complaints and generalized lymphadenitis may suggest either disease. The disease may be recognized by finding the worm on biopsy, by radiographs showing calcified worms, by the pathologic picture in tissue section, by the presence of microfilariae in the blood, and by the cutaneous test.[707] Microfilariae may not appear in the peripheral blood because of lymphatic block.[31]

African trypanosomiasis may be confused with brucellosis because of its varied and sometimes similar symptomatology Differentiation largely depends upon demonstration of trypanosomes (*gambiense* or *rhodesiense*) in lymph nodes, blood, or spinal fluid

American trypanosomiasis may present a picture of high fever, facial edema, adenitis, and cardiac weakness which may cause confusion with brucellosis Diagnosis depends upon demonstration of *trypanosoma cruzi* in blood or on animal inoculation, or on the complement-fixation reaction

Convalescence from other illness may be complicated by exacerbation of previously latent or very mild brucellosis, resulting in a complex diagnostic problem Closely following such a variety of conditions as streptococcic sore throat, epidemic grippe, influenza, pneumonia, measles, scarlet fever, other acute and chronic infectious diseases, and traumatic and surgical shock, brucellosis may produce a continuation of acute or chronic illness, systemic

tact with cattle or their freshly slaughtered carcasses, as in the Texas outbreak, may be a source of additonal confusion, since some of these individuals would have serologic evidence of *Brucella* infection of occupational origin.

Typhus fever, in its epidemic louse-borne form, should seldom present diagnostic difficulties except in the absence of known exposure to louse-borne infection. The abrupt onset, after an incubation period of six to fourteen days, characteristic eruption, and appearance of blood agglutinins against *B. proteus* (strains *OX 19* and *OX 2*), usually in the second week, usually allows an accurate diagnosis. However, there may be cross-agglutination with *B. proteus OX 19* in the presence of *Brucella* infections.

In the endemic form ("murine," "American," "flea typhus"), the less profuse rash and milder clinical course may cause greater confusion with brucellosis, because of the possible cross-agglutination reaction with *B. proteus OX 19*.

Cholera, in its mild ambulatory "cholerine" form, rarely may need differentiation. Discovery of the *V. comma* in hanging-drop stool preparations or in smears or by culture, are the means of laboratory diagnosis. Cholera may produce agglutinins against *Brucella* (p 285).

Asiatic relapsing fever may need to be differentiated from brucellosis because of similar subjective complaints, splenomegaly, and hepatomegaly. Polymorphonuclear leukocytosis is often, though not invariably, present The only certain means of diagnosis is through the detection of the spirochetes in the blood smear.[721]

Kala azar (visceral leishmaniasis) may simulate brucellosis because of the usual prolonged irregular fever, splenomegaly and hepatomegaly, emaciation, anemia, leukopenia, and occasionally generalized lymphadenopathy The parasites (*Leishmania donovani*) may be found in leukocytes in the peripheral blood Characteristic swollen monocytes or leukocytes crowded with *Leishmania* forms may be found in preparations stained by the Romanowsky method Splenic puncture or liver puncture may be necessary. Occasionally blood culture using the Nocolle, Novy,

Chapter VII

PSYCHOLOGIC STUDIES IN CHRONIC BRUCELLOSIS

Statement of Problem

AN attempt is made in this chapter to clarify some aspects of the diagnosis, differential diagnosis, and management of chronic brucellosis in relation to the psychoneuroses

It has been stated elsewhere,[304, 305] (1) that the diagnosis of brucellosis cannot easily be established or ruled out, (2) that chronic brucellosis often will give a textbook picture of "neurasthenia", (3) that there may coexist an unrelated or related psychogenic or somatic illness, (4) that emotional disturbances may be precipitated or aggravated by chronic brucellosis, (5) that these disturbances may prevent recovery from chronic brucellosis, (6) that when brucellosis and psychoneurosis coexist the physician may attribute all manifestations to the neurosis or to the somatic illness, depending upon his professional viewpoint, (7) that following recovery from brucellosis the patient may attribute to brucellosis all symptoms that remain or that subsequently arise because of unconscious unwillingness to abandon the solid ground furnished by a somatic illness for the diagnosis of psychoneurosis which he considers less tangible and more onerous

A chronic illness such as brucellosis may allow expression of emotional problems by conversion and other mechanisms in persons previously reasonably well adjusted, perhaps because of the frustrating nature of the long-continued illness Once the neurotic

or localized, that is difficult to distinguish from complications or sequelae of the preceding illness.

Other diseases coexisting with brucellosis may result in varied symptomatology which may tax all diagnostic resources. It is not infrequent that the common syndrome of fever, loss of weight, nutritional anemia, fatigue, and pallor, in the presence of laboratory evidence of brucellosis in an active or latent form, masks a far more important condition such as obscure malignant disease. Multiple myeloma, sarcoma, carcinoma, lymphoblastoma, leukemia, and myelofibrosis have been encountered under such circumstances.

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A chronic illness such as brucellosis may allow expression of emotional problems by conversion and other mechanisms in persons previously reasonably well adjusted, perhaps because of the frustrating nature of the long-continued illness Once the neurotic

manifestations have been precipitated by somatic illness, they may persist indefinitely. Weiss[102] does not believe that chronic brucellosis serves as a cause of neurosis but that it *permits the expression of neurotic manifestations.* These concepts are not very different. Removal of the permissive factor, through treatment of the infection, may be essential. It may be difficult to determine to what degree the patient is maladjusted because of illness or ill because of maladjustment.

Darley and Gordon[102] commented on the possible relationship of psychoneurosis and brucellosis. Although they felt that a situation responsible for neurotic symptoms can lead to a personality-determined illness, they did not find *Brucella* sensitization to be decidedly increased in a large group of patients with such illness. Emotional and personality factors seemed to play a significant role in the illness of 702 (46.9 per cent) of the 1,497 patients skin tested with *Brucella;* of these 702 patients, 114 (16 2 per cent) were *Brucella* sensitive, an insignificant figure when compared with the 15.7 per cent of positive skin tests for the total group of 1,497 patients. There were 588 (46 6 per cent) psychoneurotic patients in the skin-test–negative group and 114 (48 2 per cent) in the skin-test–positive group, an insignificant difference. They concluded that a diagnosis of chronic brucellosis should be challenged until the possibility of psychoneurosis has been evaluated, more or less the converse of the view of Evans,[201] who stated that the resemblance of neurasthenia to brucellosis challenges the right of a physician to make a diagnosis of neurasthenia without considering the possibility of chronic brucellosis. These views are not as dissimilar as they appear, for Darley and Gordon also stated that "the patient may have chronic brucellosis or psychoneurosis or both" and that "the presence of one does not rule out the possibility of the other."

The attempt to evaluate this intricate problem statistically may not be well-advised in view of the imperfect methods available for the diagnosis of either condition A patient with chronic brucellosis and psychoneurosis may handle his neurotic problems better after alleviation of his somatic illness.[304] Similarly (p. 377)

a patient may recover from chronic brucellosis much more readily if personality and situational problems are resolved, through such simple processes as relief from insomnia and anorexia The "either/or" attitude in diagnosis and treatment is not adequate. What one psychiatrist may consider to be a slight or unimportant deviation from the normal, another may think to be a serious character neurosis What one internist may consider to be a clinically unimportant *Brucella* allergy persisting after recovery from infection, another may find to be an active illness through demonstration of the organism in the blood stream or in a localized process

In view of the incomplete laboratory data on which the diagnosis of brucellosis often must be made (lacking positive culture) and since the diagnosis of psychoneurosis usually rests on symptoms alone, differential diagnosis may be exceedingly difficult Negative skin tests, negative blood-agglutination reactions, and noninformative phagocytic indices have been found to exist in patients in whom diagnoses of psychoneurosis have been made by competent psychiatrists, only to have new light shed on the total illness by isolation of *Brucella* from the blood or tissue or by other definite evidence of active infection

It is often found that, if brucellosis is considered at all, the only laboratory procedure used was the blood-agglutination test, [10, 11] that low titers were ignored, that high titers were considered to be cross-agglutination reactions, and that negative reactions were considered adequate to rule out brucellosis In some patients it is found that an intradermal test also was done and that the reaction was considered insignificant because "a large percentage of the population has positive skin tests anyhow," or "it only indicates an infection from which you undoubtedly have recovered since your symptoms have persisted much too long to be accounted for by brucellosis" (on the erroneous theory that brucellosis is necessarily a self-limited disease, lasting not more than eighteen months), or that the skin reaction was ignored because it did not react violently. The information obtainable from the opsonocytophagic test usually is found to have been omitted.

Seldom is adequate cultural study made on blood, urine, exudate, bile, or other fluids or tissues including biopsy material.

The experience of Evans is a classic example of failure to consider the infectious disease process when partly obscured by other symptomatology. *Brucella* had been isolated from the blood during an acute illness, which occurred less than a year after the infection supposedly was contracted. *Brucella* was again isolated from blood at a later date. Subsequently, in spite of this past history and largely because blood-agglutination reactions were negative, the possibility of brucellosis as a cause of a long-continued chronic illness was ignored. Psychoneurosis was assigned as a cause of all symptoms. Three years after the second positive blood culture, and after those years of suffering, *Brucella* was isolated from bile and from other intra-abdominal lesions.

The mere demonstration of the existence of psychoneurosis or a physician's or psychiatrist's conviction that there are problems of emotional origin are insufficient to prove the absence of continued infectious disease.

For the sake of bringing about recovery before the organism becomes physiologically entrenched and for psychic prophylaxis, early diagnosis of brucellosis is important but may not be possible. The disease is usually so insidious in onset as to escape the attention of the physician early in its course. Weiss[701] stated that one ought to be able to rule out brucellosis without too much time or trouble because of the ill effect upon the patient of leaving the uncertainty that a physical cause for the symptoms may exist. The possibility of an early diagnosis is very often precluded by the lack of cultural evidence, and the uncertainty of the remaining diagnostic laboratory procedures. Cultural study, including animal inoculation, may require as long as five and one-half months.

It may be necessary to refer patients for psychotherapy when doubt still exists of the status of the possible infectious disease. In some patients the presence of chronic brucellosis must be ignored because of the relatively greater importance of a psychiatric problem. Under other conditions, a trial of specific treat-

ment of the supposed physical illness may be indicated, deferring further evaluation of the psychic component to a later date. The solution in some of these patients is to combine expert psychiatric investigation concomitantly with clinical trial of specific treatment for brucellosis. (It is realized that this may complicate treatment because some patients may utilize physical treatment to block an elucidation of the psychodynamics of their symptoms)

Depression is frequently found among other manifestations common to brucellosis and to some psychiatric states In brucellosis depression apparently may be of toxic or organic origin or may be purely psychogenic, incident to frustration of instinctual and more superficial drives and ambitions. Neurologic as well as psychiatric study may need to be carried out, including electroencephalography and perhaps pneumoencephalography The Rorschach test alone is very likely to show evidences of true depression or to rule it out (p 393) In one patient with a history of epileptiform convulsions, a normal electroencephalogram, combined with negative evidence in the Rorschach interpretation, was of value in confirming the clinical impression of hysterical seizures concurrent with chronic brucellosis

Fatigue in patients with brucellosis may be elucidated by such combined psychologic and physiologic studies, and its cause assigned to the somatic illness or the psychologic state Alexander and Portis [9] reported results of a study of a group of psychoneurotic patients in whom fatigue, chronic or appearing in acute attacks, was accompanied by apathy, loss of zest, a feeling of aimlessness, and a repulsion against the routine of everyday life, and by a flat intravenous glucose tolerance curve In a few of the author's patients such a hypoglycemic state apparently accounted for fatigue in patients obviously suffering from psychoneurosis, with brucellosis apparently playing no important role In others, absence of such faulty carbohydrate metabolism of psychic origin and absence of evidence of psychoneurosis, helped to redirect attention to brucellosis itself as the cause of fatigue

Methods Employed

An attempt to determine the importance of the psychogenic components in chronic illness such as brucellosis was begun in 1943, first among Navy personnel and later among civilians. The procedures used were:

1. Interviews, concentrating on current complaints and history, supplemented by intravenous use of sodium amytal (narcoanalysis) in some *
2. Projective and nonprojective psychologic test procedures
   a. Cornell Selectee Index (Form C), as a compressed interview method to supplement the oral interview
   b More elaborate psychologic studies, † including the Rorschach test, figure drawing, story associated with figures, analysis of expressive movements in handwriting, thematic apperception tests, and, when indicated, intelligence testing, such as use of the Bellevue-Wechsler
3. Correlation of the psychologic with the clinical and laboratory data; (attempt was made to classify as a somatic illness or a psychologic problem, or at least to evaluate the more important of the two components when they coexisted)
4. Therapeutic test of specific vaccine therapy, in an attempt to evaluate the somatic and psychic manifestations when their coexistence obscured the problem
5. Treatment.
   a Of brucellosis uncomplicated by important degrees of neurosis by physical means (e g. vaccines, etc)
   b. Of simple psychologic problems by supportive measures, or
   c Reference to psychiatrists for more intensive therapy
6. Prolonged follow-up, including repetition of psychologic studies when indicated and of laboratory procedures

* Interviews under sodium amytal were carried out by the author in the simpler problems, and by Dr Paul Hoch in those in whom serious problems were found or suspected

† These procedures were carried out by Molly Harrower, Ruth Munroe, Camilla Kemple, and other expert psychologists

CORNELL SELECTEE INDEX

The Cornell Selectee Index (Form C) as an aid in psychiatric diagnosis, was used in the rapid evaluation of over 16,000 individuals[306, 309] during one two-year period in the naval service.

Advantages of the written questionnaire were, among others: (1) It served as a starting point to which additional information was quickly added; (2) Rarely did patients fail to answer questions truthfully, perhaps considering written falsification a more serious offense than the verbal, (3) The questions listed are those likely to be asked in any psychiatric interview, and (4) It resulted in the saving of perhaps forty-five minutes or more with each patient, the forms being executed while other patients were being interviewed. Many persons who are ill may not be detected by the use of the Index but those detected *are* ill[309]

The accuracy of the method, combined with a short psychiatric interview, was suggested by the following occurrence Fifty men from the crew of an aircraft carrier being readied for sea were sent to the author by the ship's medical officer for an opinion as to their fitness for their assigned duties, because of his doubts following superficial observation of them Forty of the men showed evidences of psychoneurosis, psychopathy, or psychotic trends after screening by the Cornell Selectee Index (Form C) and short interviews, and were referred to a naval hospital for further observation and evaluation by more orthodox methods. After from 2 to 6 weeks of observation, the tentative diagnoses were confirmed in all

In the present study this method helped to confirm the clinical impression of the patient's personality in many instances, additional confirmation was obtained by further interviews and by the projective tests.

PROJECTIVE TESTS

Rorschach tests, usually with additional psychologic studies, were performed on 72 patients with chronic brucellosis, usually because of special emotional problems but in some instances as

a routine measure, in an attempt to determine what pattern, if any, patients with chronic brucellosis might exhibit.

The validity of personality interpretation based on Rorschach tests, figure drawing, and associations to figures drawn,[452] and analysis of expressive movements in handwriting, when expertly interpreted, has been established. It was considered essential to utilize the help of only the expertly trained and experienced psychologist or psychiatrist for interpretation of these procedures For example, organic brain disease was suspected in one patient from the Rorschach findings by a psychologist who administered the test while in process of training. She sent the record to an expert who saw no evidence of brain pathology but concurred in the diagnosis of anxiety hysteria. The lack of organic brain pathology was confirmed by further study.

No data concerning the patient were given to the psychologist who was to administer and interpret the tests, the psychologist being told only that a possible problem in a patient with brucellosis was to be evaluated. This practice was adopted to help instill in the patient confidence not only that the study was important but that it was unbiased by the author's or psychologist's personal viewpoint. No additional information was furnished, except in instances when special attention to some phase was desired, such as in suspected psychosis.

In one patient not only was no information given to the psychologist but the patient was not even seen by her, the test being administered by her assistant As in virtually all other patients, the interpretation complemented the clinical impression obtained by the author. This patient exhibited a serious behavior problem (compulsive promiscuous sexual behavior) and perpetuation of symptoms originally referable to brucellosis Clinical impression was of a character neurosis, with a large homosexual component Use of the Cornell Selectee Index (Form C) had tended to confirm this impression The psychologic study brought out additional evidence of latent homosexuality and obsessional neuroticism, expert use of narcoanalysis further confirmed these

points and the urgent need for psychoanalysis, which was then undertaken.

In one patient who could not have the advantage of the battery of psychologic studies at the hands of an expert, the data from a self-administered Rorschach were sent for interpretation. The report, although necessarily less complete than usually obtained from the personally administered tests, was helpful in confirming the diagnosis of an important psychologic factor in the production of some symptoms in a patient with a severe chronic *Brucella* infection (p 219). The confirmation that this patient's illness was complicated by personality factors did not lessen the importance of the chronic *Brucella* osteomyelitis from which she had suffered intermittently for years, nor the necessity for continuing the successful, specific therapy. She was able to handle her emotional problems better after realizing their significance.

Narcoanalysis is useful only in the hands of the well-trained and experienced psychiatrist. In one patient (p 379) narcoanalysis was attempted by the author because of practical considerations in the hope of supplementing the material furnished by interviews and the psychologic studies. It was utterly sterile, the patient blocking completely or maintaining such guarded control as to prohibit free association In another patient, in whom the clinical and Rorschach study had indicated a very severe personality disorder, without overt evidence of psychosis, a skillfully conducted interview under intravenous sodium amytal brought out unmistakable evidence of auditory hallucinations and delusional thinking

No pretense is made that this study is complete Other technics will be included in further investigations It seems important that such studies be made from the viewpoint of the internist as well as the psychiatrist and psychologist and that a blending of viewpoints be achieved.

Similar combined clinical and psychologic studies in chronic illness have been made by others

In postvaccinal (yellow fever) hepatitis there is great symptomatic similarity to chronic brucellosis, as well as similarity in the

problem of management. Benjamin and Hoyt[51] commented on the psychiatric findings as follows: "The final opinion [of the psychiatrist] was that the individuals were disabled by a neurosis which had become latent but which was re-kindled and made manifest by an organic physical illness. . . . The gastrointestinal symptoms were considered to be a continuation of those of the acute illness unconsciously prolonged as an escape from a difficult situation."

Psychologic effects of recurrent malaria were discussed editorially in the *J.A.M.A.* (130:938, 1946). The Rorschach technic demonstrated mental apathy as an expression of fatigue and thus corroborated the clinical impression of lowered vitality, initiative, and interest. The symptoms complained of in the 50 patients under observation were: weakness or fatigability, 94 per cent; intolerance to heat, 92 per cent; tension, 78 per cent; chronic headache of the tension type, 45 per cent; insomnia, 45 per cent; "blackouts" and palpitation, 40 per cent; and splenic tenderness, 27 per cent The authors stated that a correlation of these symptoms with physical condition, personality adjustment, and malaria showed that a considerable portion of the symptoms could be attributed to the recurrent attacks of malaria alone. The best adjusted and least debilitated patients had relatively few complaints except weakness and fatigability after exercise. The patients who adjusted poorly in civil or military life made poor adjustments to the recurrent attacks and became incapacitated early with a wide variety of symptoms. The adjustment of the individual to the stresses of illness and concurrent situational factors contributed to the development, perpetuation, and intensification of the symptoms of chronic malaria.

Case Histories

The following case illustrates the error of considering an illness to be purely psychogenic or purely somatic and the difficulty in management of either component.

A 21-year-old unmarried girl had a prolonged period of vomiting, attended by loss of weight, low-grade fever, and fatigue in 1934. The

condition was ascribed to anxiety hysteria because no physical findings were evident and because of personality and environmental factors. In 1936 it became evident that this patient was suffering from chronic brucellosis. Because of the similarity of many of her symptoms to those previously exhibited and the excellent response to *Brucella* vaccine therapy, it was then considered that her previous illness had probably been on the same basis and that the diagnosis of psychoneurosis had been an error. She gained 15 pounds in weight, temperature became normal, and her former great energy returned, concomitant with excellent phagocytic response.

She left her unhealthy home surroundings shortly after this improvement was established and remained well and happy for about eight months. At the urging of her foster-mother she returned home; relapse very soon followed. She rapidly lost the weight she had gained, symptoms partly referable to psychoneurosis (and undoubtedly also partly referable to recurrent chronic brucellosis) returned. From that time on she was resistant to any physical therapy. Marked sensitivity to *Brucella* vaccine developed.* Her psychologic state, with hysterical manifestations and regression to more immature behavior levels, was worsened by subsequent illness and by added psychic traumas (breaking of her engagement, death of her own father under tragic circumstances, and death of her loved foster-father) which robbed her of all sense of security. By then it was evident that there was an important correlation between physical and psychic illness.

She consented to have psychotherapy, with great reluctance. Cooperation with her analyst was poor. She expressed the fear that extremely unpleasant memories of past events would be uncovered. She had vague recollections of brutal treatment at the hands of her father, she thought that on one occasion he had placed her on a hot stove during a drunken rage. Also she desired to preserve intact her memories of and respect for her mother who had died when the patient was 6 years old. She expressed fear that further probing would bring forth evidence of lack of sweetness and fineness with which she had imbued her, in fantasy.

After a few months of psychotherapy she developed a succession of grippelike febrile illnesses culminating in a severe attack of meningoencephalitis, in all probability attributable to *Brucella* infection, al-

* Apparently allergy may be intensified by some ill-understood psychologically influenced mechanism (Harris, H. J., The possible influence of psychologic factors in *Brucella* allergy. *Int. Arch. Allergy & Applied Immunol.* In press.)

though unproved by culture (p 238). Following this illness she evidenced further regression to even more immature reaction levels Convalescence from the meningo-encephalitis and the still active chronic brucellosis seemed to be measurably slowed by her refusal to eat normally and by insomnia which was aggravated by nightmares, depression, fear of death and of the dark. Then, at a time when sleep was improving and her phobias lessening, a succession of further personal tragedies (suicide of one relative and sudden death by natural means of another) was followed by intensification of all her abnormal psychologic reactions

A Rorschach study was reported as follows: "There is no indication in this record of the type of personality change which has come to be associated with cerebral damage. It would seem to me therefore extremely unlikely that organic factors could be responsible for any psychological difficulties which this patient may exhibit. [Electroencephalogram had showed some abnormal waves, referable to postencephalitic changes (p. 240)] In fact, in marked contrast to the stereotyped and undifferentiated personality picture presented by the individual with brain pathology this patient shows some acute personal problems which must be considered neurotic in character. There are indications of the hysterical type of personality.

"Among some of the outstanding features of the personality are the following marked insecurity and the residue of some psychic trauma, the capacity for good rapport with her environment, but a *too-labile emotionality which may sometimes overcome* her control There is also the capacity for a creative fantasy, but this is negated by the fact that she is afraid of and, to some extent, represses her inner life This is an individual with considerable drive and energy who has not yet succeeded in directing her psychological powers into satisfying channels, and is in consequence disturbed by their misdirection"

A condition not unlike anorexia nervosa furnished an adequate barrier to recovery She used every conscious and unconscious mechanism usually encountered in persons who do not want to gain weight, resulting in a diet deficient in basic elements, calories, and vitamins In addition, insomnia became more marked as an added reason and excuse for lessened resistance to infection Apparently the continued infection, a threat to the organism as a whole, increased the sense of insecurity which was based on adequate factors in her remote and

recent history A further attempt to induce her to have psycho peutic help early in 1946 led to one interview with a psychiatris reported that he had not considered her problem urgent and th need not see him if she did not care to The psychiatrist repor the author that he considered the problem an urgent one

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The second case illustrates the coexistence of psychone and brucellosis, the difficulties in evaluating their individual and in achieving recovery·

A 27-year-old unmarried girl was first seen in 1941 becaus diagnosis of brucellosis established a year before by Wainwrig later considered that the diagnosis was an error and that the illness was due to psychoneurosis and personality disorder C basis of further clinical study the author reverted to the original nosis of brucellosis for which the patient received treatment marked although rather slow clinical and serologic response. Al year later the patient developed an acute, nonvenereal pelvic tion The surgeon in attendance, not realizing the possible conn between *Brucella* infection and salpingitis, nor the possibility would yield to conservative measures such as a combination of wave pelvic diathermy and *Brucella* vaccine, removed both fal tubes and one ovary which were found to be inflamed Foll operation many of the symptoms previously complained of rec including fatigue, malaise, and low-grade fever. There was agair clinical and serologic response to *Brucella abortus* vaccine but of semi-invalidism persisted

The psychologic study was reported as follows: "The Rorschac ture of this subject is very unfavorable, suggesting anxiety ne with a depressive mood and probable hypochondriacal trends are perhaps schizoid tendencies but at the present time the pr seems more of neurotic self-absorption than of a schizophrenic p The possibility of such a process should, however, be kept in m

"She is very much blocked, unable to mobilize her resources q

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However, she seemed to gain some insight as the result of that one interview and perhaps through the glimpses into her problem achieved through her interviews with the analyst three years before. Her diet became more adequate, she gained weight, and depression and gross evidence of phobias lessened. (See pages 237, 426.)

The second case illustrates the coexistence of psychoneurosis and brucellosis, the difficulties in evaluating their individual roles, and in achieving recovery.

A 27-year-old unmarried girl was first seen in 1941 because of a diagnosis of brucellosis established a year before by Wainwright. He later considered that the diagnosis was an error and that the entire illness was due to psychoneurosis and personality disorder. On the basis of further clinical study the author reverted to the original diagnosis of brucellosis for which the patient received treatment, with marked although rather slow clinical and serologic response. About a year later the patient developed an acute, nonvenereal pelvic condition. The surgeon in attendance, not realizing the possible connection between *Brucella* infection and salpingitis, nor the possibility that it would yield to conservative measures such as a combination of short-wave pelvic diathermy and *Brucella* vaccine, removed both fallopian tubes and one ovary which were found to be inflamed. Following operation many of the symptoms previously complained of recurred, including fatigue, malaise, and low-grade fever. There was again good clinical and serologic response to *Brucella abortus* vaccine but a state of semi-invalidism persisted.

The psychologic study was reported as follows. "The Rorschach picture of this subject is very unfavorable, suggesting anxiety neurosis with a depressive mood and probable hypochondriacal trends. There are perhaps schizoid tendencies but at the present time the problem

She tries to be controlled, guarded, evasive, to display nothing of her real feelings or thoughts. She is not able to put up a flexible defense, however. Her responses in the test come slowly and while they look innocuous on the surface, the technical Rorschach scoring shows up the basic difficulties. While she can usually keep herself from going to pieces, it is doubtful whether she has enough energy left over for productive activity. Apparently she responds relatively well to outside stimulation. She may fear social contacts initially and may not always handle them well. Nevertheless her anxiety and depression seem to be somewhat lessened when she is not left too much to her own devices.

"She is emotionally very immature, with strong biological drives. The latter are too much a source of anxiety to be expressed freely There must be a constant conflict between an impulsive, assertive nature and fear of impulsive expression. She starts out boldly, but soon becomes insecure. She is sexually narcissistic—perhaps preoccupied with sex on an immature level, certainly body conscious to an unusually high degree Her image of the male is extremely effeminate and weak At a guess the mother plays a dominant role—a role possibly characterized by the 'massive black spider' seen in card IV. [The psychologist did not know the mother and had no data concerning the patient]

"The prognosis seems poor unless intensive psychotherapy is undertaken."

Clinically it was evident that the illness had become a means of escape She was still subject to her mother's whims and orders, under *all circumstances She was told when to go to bed, what and when* to read, when to arise. Occasionally she rebelled in a childlike way, stamping her foot and saying that she would not, but she always did

She obstructed every attempt at psychologic rehabilitation Although she seemed to understand that her home environment was responsible for her extreme immaturity and her many psychoneurotic manifestations, one excuse after another for failing to rectify the situation was advanced She would agree that she should take a position which would allow her to lessen her dependence upon her mother, to support herself, and to have psychotherapy She would go far enough to spend week after week searching for jobs, with apparent sincerity Whenever a position was offered which was within her intellectual

and physical ability, she would find some excuse for turning it down. During these job-hunting episodes she demonstrated her ability to carry on far more physical exertion in social activities than she had admitted to have been within her ability. After many months of self-deception she finally stated that she realized she did not want a job and that she would not leave home She had developed sufficient insight to realize that the protection of her mother was what she wanted, consciously and unconsciously, and that she was using her great filial devotion as an excuse for her refusal to sever the umbilical cord.

The patient continued to have malaise, fatigue, and low-grade fever. Her phagocytic index remained at a high level, showing a satisfactory degree of resistance to *Brucella* infection. She complained of recurrent bilateral pelvic pain and tenderness. Every menstrual period was a great event, attended by bed-rest and great maternal solicitude. Various gynecologic consultations showed moderate to marked enlargement of the uterus and adjacent tissue She spent periods of from days to weeks in bed because of the pain On several occasions the surgeon was on the point of urging further operative interference, with removal of the remaining ovary He stated on two occasions that the improvement in the pelvic findings was so marked and rapid that he felt that he must have been in error in his previous estimate of only a few days before. There was no increase in fever, white count, or sedimentation rate during these attacks. The author felt that they were of congestive origin, related to the biologic drive which she had never fully expressed, and that the scar tissue following surgery impeded the natural recession of congestion Conflicts, with severe guilt reaction, were evident Although separation from the harmful home influences, psychotherapy, and interesting work were the basis of the advice given her, the nearest to fulfillment was the taking of an uninteresting job with very small salary which allowed her to remain under the care and protection of her mother

The symptomatology, originally referable to *Brucella* infection, apparently became useful to the neurotic, immature patient in an attempt to avoid a more mature behavior pattern, which would have meant the assumption of responsibility Pelvic localization of pathology, which seemed to be neither infectious nor inflammatory, apparently was determined by psychic factors involved in a repressed strong biologic drive.

That superficial psychotherapy or passive acceptance of the physician's viewpoint was not without effect was shown when this patient had mild recurrence of bilateral pelvic pain in August, 1946. Tenderness was elicited on pelvic examination but without evidence of induration or other manifest pathology. The patient remarked: "It is possible that this upset is due to an emotional state. I am in love and in a most uncertain state of mind." Complete blood study suggested continued freedom from infectious disease. In January, 1947, she stated that she was about to accept a position away from home since she felt entirely well and had come to accept the idea that the psychic factor had been of paramount importance in the latter part of her illness. She was not willing to believe that her mother had played a dominant role in its causation, however. She was still well in January, 1948.

The third case illustrates a physical illness which at first seemed paramount, where a psychologic as well as a somatic component became evident, with improvement in both through treatment of brucellosis alone

A 35-year-old married woman had had symptoms of chronic brucellosis for three years She considered herself "just neurotic" until she discovered that she was running a fever. She was extremely nervous, depressed, irritable, "achey," and thought that she was having colds all winter, although only occasionally with rhinitis or other evidence of an actual cold Temperature was seldom as high as 101° F, usually from 99 6 to 100° F. Blood-agglutination reaction with *Brucella abortus* had been positive in a low dilution and a skin test done on the same day had been violently positive. Her phagocytic index showed a moderate degree of resistance to *Brucella* infection Response to *Brucella abortus* vaccine was satisfactory, clinically and serologically, but symptoms and low-grade fever continued in a lesser degree. The psychologic study was reported as follows.

"This subject apparently has a neurosis associated with bodily symptoms While the protocol is not without signs of more deep-lying conflict, it is probable that her physical illness has played a preponderant role in the development of the neurosis or at least strongly conditions

her reactions at present. She suffers also at the present time from strong feelings of insufficiency, pervasive but controlled anxiety, and depressive moods for which she often tries to substitute a spurious cheerfulness . . .

"The personality is on the whole rather well-integrated and for the most part skillfully disciplined. . . . Apparently there is some confusion in the sexual sphere—something like a critical distrust of feminine feelings and some inhibition of expression, though probably no overt problem. At a guess some preoccupation with the idea of pregnancy, perhaps associated with anxious feelings of insufficiency. [An excellent "guess"; this patient greatly desired pregnancy which was rendered undesirable by possible hereditary epilepsy in the husband.]

"These problems seem to be deeper than practical concern about her illness. One may guess that the illness precipitated problems which might otherwise have gone unobserved and that real anxieties are now being used both to express and to cover up neurotically determined anxieties.

"Just how far the neurotic picture now determines or perpetuates physical symptoms, it is impossible to say. The neurosis does not seem to be severe, but with symptoms all ready at hand in her brucellosis it may find more troublesome expression than would normally be expected. Physical illness would make a very convenient defense against the problems suggested above—one which she would be unconsciously tempted to continue beyond realistic need. Psychotherapy might contribute importantly to her general recovery."

Further search for focal infection led to discovery of a tender, palpable fallopian tube and enlargement of the right ovary. Following treatment with ultrashort-wave pelvic diathermy and continuation of *Brucella* vaccine, there was resolution of the pelvic pathology and the patient seemed to make a complete recovery. By then it had become evident that each recurrence of symptoms had been preceded by a significant drop in the phagocytic index (as frequently observed in other patients), and that she had been free of symptoms during such periods as her resistance remained at satisfactory levels.

For the past two years this patient has remained well and with a continued high phagocytic index—without vaccine or psycho-

therapy. It seems apparent that better health has allowed better adjustment.

The fourth and fifth cases illustrate common physical manifestations and fruitless searches for a physical cause:

A 35-year-old married woman complained of joint and muscle pain, headache, weakness, nausea, and vomiting of several years duration for which she had been studied at various hospitals and clinics. Diagnoses had been fibrositis, arthritis, and psychoneurosis Rigid diets and meticulous care of the bowel, to which she adhered rigidly and willingly, had been prescribed. She greatly desired a diagnosis of a somatic illness. Psychotherapy was abhorrent to her. Sexual adjustment during ten years of marriage had been poor; she was frigid. Laboratory tests for brucellosis were equivocal, perhaps due to previous intracutaneous tests with *Brucella* antigen. Her psychologic study indicated personality disturbance of moderate severity; immaturity of inner development, anxiety, tension, hypochondriacal trends, and disturbance at a deep level in the sexual sphere.

She refused reference for psychotherapy but seized on the slight doubt that remained as to existence of brucellosis to ask for a trial of treatment (a procedure of questionable merit in this instance). She described reactions so bizarre as to be unmistakably hysterical There was no improvement. She resumed the search for physical means of cure, unable to accept the assurance that brucellosis and other physical illness had been ruled out.

In this patient the need for physical expression of her psychic turmoil apparently was so great as to preclude her abandonment of symptoms under any circumstances When she was denied further treatment of her self-diagnosed brucellosis she sought the services of a chiropractor who demonstrated many "subluxations" and promised a cure. Significantly, she did not improve under chiropractic treatment No "faith cure" seemed possible, so severe was the emotional disturbance.

A 31-year-old male business executive gave a history of fatigue and joint and muscle pain of fifteen years duration, for which no cause had been found after repeated study. His tests for brucellosis were

equivocal, indicating a probable past infection but no definite evidence of present illness. This patient saw the difficulty in distinguishing between such a chronic infectious process and a psychoneurosis He seemed willing to consider the possibility of neurosis if physical factors could be ruled out. A brief psychiatric history was supplemented by execution of a Cornell Selectee Index, a Rorschach test, figure drawing, and analysis of expressive movements in handwriting Meanwhile a therapeutic trial of *Brucella* vaccine was made in an attempt to strengthen the diagnostic evidence. There was no improvement following this in spite of an excellent serologic response. The psychologist's report included the following observations:

"This protocol presents a rather typical picture of the superficially adjusted neurotic, where psychosomatic symptoms are common (though they do not rule out brucellosis or other chronic illness). . . . Features of evasion and carefully controlled anxiety are prominent . . . He is on the emotional side As he himself remarks, the recurrence of maps (often suggestive of evasion) may be in this case related to a conscious desire to travel Very probably, however, the roots of this desire are also an unconscious wish to get away from it all into a more colorful, fanciful world with fewer psychological and realistic exigencies Since he has far too sound a reality sense to believe fully in this kind of escape, the consequence is continued good adjustment with a pervasive, subacute anxiety. . . The pattern seems to be a rather hollow ambition, functioning not too successfully as an escape from distressing moods The tension between a rather romantic striving, the futility of which he knows in advance and feelings of depression or insufficiency can easily result in the conscious experience of fatigue . Instinctual needs are strong but conflicted and inadequately integrated with his conscious image of himself at the most superficial level Specific conflicts of a not uncommon nature can be discerned oral dependency needs and aggressive trends which are incompatible with each other and which are *both* largely repressed Sexual uncertainties are evident His attitude toward women seems highly ambivalent They are powerful but insecure, aggressive but perhaps intellectually contempt-worthy The male does not come off so well either In his figure drawings the man is much smaller than the woman but his proportions are better and he is drawn more firmly. He is described, however, as 'solid' and 'irresponsible' This contradiction in adjectives probably expressed pretty well the Rorschach con-

stellation. Perhaps basically because of sexual conflicts, this man seems to have added up himself as both solid and irresponsible, unable to work out a mature relationship between an adequate sense of reality demands and overinflated, romantic strivings. This contradiction when held in check by a 'good adjustment' may easily show primarily as fatigue and other bodily symptoms This patient seems a good treatment risk for psychoanalysis but many people get along with this type of personality picture without analysis"

Interviews with this patient, before and after the psychologic study, brought out additional data which agreed with the results of the study. He stated that his parents were old when he was born and that he had no companionship. His mother had coddled him, "tied me too close, I couldn't get away from it . . . Because I had curly hair, they kept it so until the first grade in school—and I was a sissy. I know that has been quite an influence that I have been fighting against . . . I have always had the feeling of instability because I have never been able to get ahead of the game My sister has been ill and my wife is ill. My wife is an extrovert—a good contrast to me—she tries to get me to be less concerned but I can't do it."

He was unable to accept the large amount of evidence against an infectious process and the virtually conclusive evidence of psychic illness. To have psychotherapy urged upon him, after dispassionate explanation had failed to convince him, would have been fruitless and probably unwise in view of an already weakened ego. He was seen again about a year later, in much the same state

The sixth case illustrates the usefulness of treatment of chronic brucellosis even in a patient with a severe psychologic disturbance.

A 35-year-old professional man of unusual intelligence and ability was referred for an opinion as to the possibility of brucellosis as the cause of bouts of intense fatigue low-grade fever, joint and muscle pains, and headache, of several years duration There was a long history of alcoholism The clinical impression was of possible *Brucella* infection and of a character neurosis Laboratory study confirmed the probability of chronic brucellosis but Rorschach study revealed a

type of intellectual and personal deterioration such as is commonly seen in organic brain disease, also with indications of abnormal, bizarre, symbolic thinking that is associated with a psychosis There was evidence that the patient sensed the weight of his own inadequacies, failures, and virtual crumbling of his abilities, and looked upon the affliction as in some way associated with personal guilt The general picture was one of an undermining of the personality and perhaps of more serious disturbance in thought process The psychologist appended the question. "Could he have some acute disturbance that is producing an organic or toxic psychosis?"

There were two possible sources of an organic or toxic psychosis—alcohol and *Brucella* infection. He was asked to avoid alcohol completely and a course of *Brucella* vaccine was begun, with prompt clinical and psychologic improvement. History indicated that during previous periods of abstinence from alcohol, there had been no improvement in his physical condition

Eight months after the first Rorschach test it was repeated with evidence of "tremendously favorable changes . . . one can say that he has got to the point where he is the master, instead of the slave of his ideas and impressions he is sufficiently free so that some of the difficulties centering about his basic sexual problem can come to light . "

He was encouraged to see a psychiatrist at this point Therapy on a quite superficial plane was carried out and he was able to return to his work with relative freedom from self-accusation and condemnation

An improved physical state apparently helped to bring about an improved psychologic state, in which he was able to face his problems with greater equanimity The solution was only a partial one More than a year later he decided to undergo psychoanalysis, which is in progress, with a fair prognosis

Case number seven illustrates the value of a psychologic study in strengthening a clinical diagnosis of psychoneurosis in a patient who sought a physical means of escape from an intolerable emotional problem

A 45-year-old married woman was referred because of attacks of faintness and extreme fatigue, recurrent for about eight years, with occasional gastrointestinal upsets. She had spent three weeks in bed on one occasion and required about four months for complete recovery from one attack of fatigue. Various diagnoses had been deficiency of hydrochloric acid, hypothyroidism, menopause, and hypoglycemia. She had persuaded her family physician to carry out intradermal tests with Brucellergen and to administer Brucellin in spite of lack of clinical or laboratory evidence of brucellosis. She reported bizarre reactions.

Physical and laboratory findings, including glucose-tolerance tests, were negative or within normal limits. She was told that there was no evidence of brucellosis, past or present, and that her symptoms were on an emotional basis. She was able to accept this explanation. She discussed family financial reverses, and sexual inadequacy in the husband. His sexual inadequacy left her with extreme nervous tension. She recalled that her first attack of supposed hypoglycemia coincided with the arrival of a relative who was to live with her.

Excerpts from the psychologic study were as follows: "This is a gifted, intelligent and versatile woman with marked creative ability and artistic sensitiveness. She has a wealth of inner resources and is able, in general, to live in a constructive and colorful way. However, again and again, I have seen such people literally swamped and sunk by their own too-accessible fantasy. Her unconscious is too near, it can overwhelm her with moods beyond her control. As long as she has control she can tap it for her own use, but there seems to come a point where it gains the upper hand, and renders such creative people as she a prey to their own assets . . . If one gets a little nearer the heart of the disturbance that has precipitated the present crisis one finds many unsolved sexual conflicts . . . In other words, there is in the masculine concept, an irrational fear of sensuality, sufficiently strong to distort and warp her otherwise keen and critical intelligence . . . For all her superficial acceptance of the sensual, she has not reached a deep sexual adjustment. . . . She has not built around her a barricade of inhibiting anxieties, hence she feels the full force of her disturbance. On the other hand she has vast potentialities which could be tapped, and many well-established environmental contacts. She is a rich personality. I believe one could confi-

dently recommend a cautious analysis, cautious in the sense that the almost too available unconscious would have to be at first restrained But she is certainly capable of insight and, I imagine, much help"

Her figure drawings (Fig 41) helped to confirm the lack of inhibitions and other points brought out in the Rorschach analysis Psychotherapy was impractical for financial reasons.

A psychologic study of the husband tended strongly to confirm the reasons for the wife's reaction pattern Among other things, it showed banal thinking, lacking all originality, unresolved sexual problems with attempts to ignore and minimize them, unresolved guilt, lack of normal aggression, a correspondingly strong passive component, and probable lack of capacity for insight. His figure drawings are shown in Fig 42 An interview brought out the enormity of the problem In commenting on his business reverses he expressed confidence that he was adequate in business but then added thoughtfully. "But occasionally a little voice asks 'are you?'" He realized his sexual inhibitions, ascribing them to his early environment. In discussing the effect of alcohol he remarked that it did remove some of his inhibitions as to sexual activity, saying "I guess it lets you forget to avoid it"

The symptoms in the wife were dissipated, probably through acceptance of the opinion that physical illness could be ruled out and that adjustment to, or compromise with, her marital problem should be sought.

Case number eight illustrates severe psychoneurosis, active chronic brucellosis, and better psychologic adjustment following recovery from brucellosis

A 30-year-old man had evidence of recurrent active brucellosis for a period of three years *Brucella* vaccine made from mixed strains had been given and resulted in many sterile abscesses and little clinical improvement A long course of fever therapy also had not brought about recovery

Use of *Brucella abortus* vaccine in suitable dilutions resulted in desensitization and clinical and serologic improvement There was lessening of his depression as well as of lameness and fatigue and he gained weight However, within a few months there was a "return of that old despondent feeling," which lessened when he returned to his

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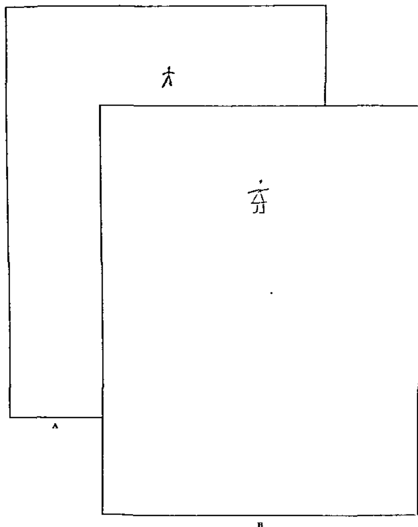


Fig 42 A and B Figure drawings made by husband of patient whose drawings are illustrated in Fig 41 A and B Marked inhibitions are evidenced Note tiny stick figures and placement on sheets of paper

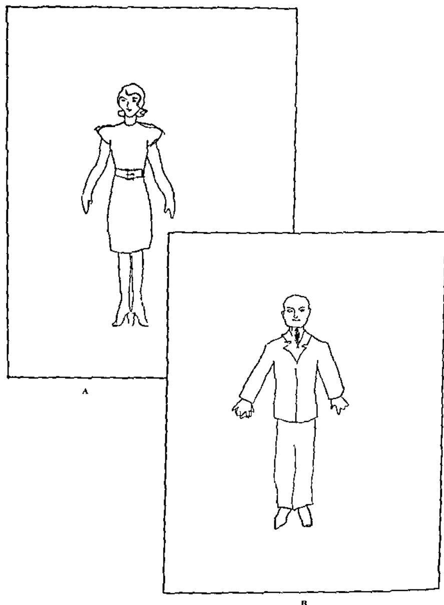


Fig 41 A and B Figure drawings made by female patient with conversion symptoms, in absence of inhibiting anxieties Note full use of sheets of paper for well-balanced drawings (Compare with Fig 42 A and B)

He again refused psychotherapy, asking for further time to work out his problems with the aid of better health which followed treatment of his brucellosis. Eight months following his first Rorschach test he stated that he was doing quite well—that he became jittery only occasionally and for shorter periods of time. A second Rorschach test was reported as follows:

"The second protocol from this subject is strikingly similar to the first in many respects Certain important changes are observable, however. The first is the dropping out of almost all of the items previously cited as suggestive of an incipient psychotic process. The distribution of number of responses per card is now quite normal, the 'suspicious' content has largely disappeared. . . . The *neurotic* solution remains, and is perhaps intensified. . . ."

His own estimate of improvement was confirmed by follow-up for eighteen months.

The ninth case illustrates the reverse of the usual situation: a patient with active brucellosis who greatly desired a psychiatric diagnosis; also illustrated is the help afforded by the psychologic studies in evaluating depression

A 39-year-old married woman stated that there was nothing wrong with her physically but that she was suffering from a serious emotional state Her main complaint was depression, she cried a great deal, and often was unable to eat or sleep Her only recourse was to alcohol which she used compulsively, allegedly in moderate amounts. Her childhood had been unhappy with a dominating mother and marked feeling of inferiority engendered by the attitude of parents and siblings. She had been unduly fat. She had married, as an escape, and had spent ten unhappy years with a domineering husband. She had divorced him and had remarried, this time with good sexual adjustment She stated that one of three sisters, who had shared the same raw milk supply for years, had developed chronic brucellosis and had suggested that she too might have it, but the patient was sure that *she did not* She verbalized her great hostility toward this sister. She had had a history of salpingitis of apparently nonvenereal origin, with salpingectomy and partial hysterectomy, recurrent thrombophlebitis alternating between the two lower extremities, she also complained

regular work and became intensified again a few months later. The coexisting neurosis had been discussed with him but he had avoided reference for diagnostic study or therapy. He volunteered the remark: "The neurosis has returned—kind of a depressed feeling, as if there is something wrong in my upper story—that's what I'm really worried about. I've always tried to hide my nervousness. It is even affecting my wife now. There is friction all the time. . . ."

He consented to a psychologic study, excerpted as follows: "This subject seems 'naturally' quite aggressive, assertive, and almost hysterically responsive to surroundings Unfortunately aggression is a source of terrific conflict for him, apparently largely through unconscious fear of retaliation. His initial response to a situation is (typically) prompt, adequate, and on the assertive side, but is immediately followed by a modification of the assertion in the direction of innocuous or even childlike behavior, and finally by acute fear where he sees himself the victim of aggression from others, helplessly exposed to attack . . . Probably he has a tendency to obsessive rumination on a situation, trying to work out an acceptable stance for himself including a reasonable assertiveness and controllable emotionality.

"Thus far the picture is essentially neurotic, but there are disturbing features suggesting the possibility of an incipient psychosis One of these is the tendency for the constructive effort to peter out. . . Thus his poverty in spontaneous responses must be attributed to a failure of effort rather than to special difficulty with the card

"The quality of the later responses in the shaded cards is also suspicious eyes in the dark, maps of land-locked lakes, repeated with at least a tendency toward the anxiety-indicating k elements in scoring; inhibition of human movement which a man of his ability should see. The squashed insects and battered leaves also suggest some sense of losing his grip. . . It may be suspected that the man is discouraged to the point of giving up and seeking a solution in schizophrenic withdrawal. .

"His mood is often depressive and anxiety-laden He carries a burden of depression and anxiety even at his best Body-preoccupation is rather prominent. .

"Indeed it is chiefly by contrast with his usual intellectual vigor that the responses cited as potentially schizoid take on their threatening character . ."

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"Indeed it is chiefly by contrast with his usual intellectual vigor that the responses cited as potentially schizoid take on their threatening character. . ."

though the urgency of treatment of the *Brucella* infection could not be doubted It was planned to use more dilute vaccine to avoid any reaction but she became more and more difficult as a patient, found excuses to defer appointments and formed a great antipathy toward the author and the method of treatment She reported a dream in which the author was a dentist with a drill, the torture of which he forced her to endure Before it could be decided how to proceed further with the problem she asked if the vaccine could not be given by her family physician When told that it could be, provided that she would report periodically for observation, she was elated. Apparently she had not the courage simply to refuse treatment as would a more mature person. As soon as she was referred to her family physician she stopped treatment. He reported several months later that she was improved.

This patient rejected a diagnosis of brucellosis although it was clear-cut In retrospect it was apparent that, before she had treatment, the reason for her rejection of the diagnosis should have been fully established In all probability it was related to her sister who had recovered from brucellosis and with whom her relationship had been antagonistic since childhood Psychotherapy properly should have preceded or been concomitant with treatment of her brucellosis, although the latter was at least partially successful.

The next case illustrates coexistence of brucellosis and psychoneurosis and the value of the various projective technics in emphasizing the importance of the psychic component.

A shy, subdued woman of 40 was referred with a diagnosis of chronic brucellosis of three years duration, complaining of excessive fatigue and "nervousness" She had had two extremely unhappy marriages and was now living "contentedly" with an elderly third husband Tests for brucellosis were not definite in distinguishing between continued active infection and clinical recovery with persistence of psychoneurotic manifestations Her Rorschach interpretation alone was helpful in understanding this inhibited patient in whom physical symptoms might understandably be a welcome means of emotional expres-

of fatigue. There were periods of low-grade fever. Tests for brucellosis were positive. A psychologic study is excerpted as follows:

"This protocol does not suggest the typical picture of depression at all. A 'real' depression, neurotic or psychotic, involves a reduction in available psychic energy which shows itself in a constricted Rorschach performance. The typical depressive picture is rather stereotyped, often with carefully exact form. This subject has an unusual number of original responses . . . and is easily stimulated by her surroundings . . . another feature definitely not found in a true depression

"It probably would be more correct to say that she is very anxious and unhappy. The conscious, or quasi-conscious, effort to control very strong impulses and affect may lead to a kind of blocking which simulates 'depression.' It is easy to imagine that she feels bad but I think a psychiatric diagnosis can be ruled out if the Rorschach is to be trusted.

"Anxiety is more prominent and it has a dysphoric tinge . . . Probably the anxiety is mostly free-floating—i e, a vague uneasiness readily attached to transient stimuli. . . .

"She does *not* give the dried-up anatomy responses I have come to consider characteristic of the old brucellosis cases. Instead she gives one or two real organs 'from the color' I would like to offer the *speculation* that this woman is not yet resigned to her illness, hence perhaps a subjective experience of depression [See comments as to her refusal to believe that she had brucellosis, in spite of adequate clinical and laboratory evidence] One might think of the disease as throwing a monkey-wrench into her previous modes of adaptation, introducing real frustrations and bringing conflicts into new focus . . ."

Treatment of this patient's brucellosis was undertaken with the hope that improvement in the physical condition would help in resolution of some of her problems There was focal and systemic reactions to vaccine (given in larger than necessary dosage initially), with swelling of some of the superficial veins previously involved in the thrombophlebitic process and of the legs in general She vomited and had diarrhea for two days following each of two doses of vaccine. She felt much worse in all respects, including depression It was questionable whether good judgment had been used in initiating treatment of the physical condition rather than to first refer her for psychotherapy, al-

whole sheet of paper, just as in the Rorschach, she is content to use, and only feels safe with, the small detailed areas in the blots She is a person who has definitely circumscribed activities, somewhat stiff,

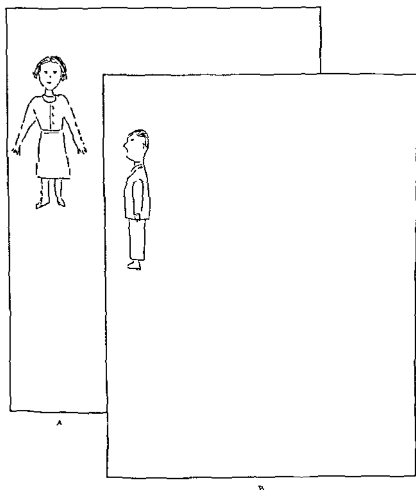


Fig 43 A and B Figure drawings See description in text

and lacking in spontaneity. She does not dare to be spontaneous because that might incur disapproval She wants to be correct and to do the right thing In speaking of her drawings she remarked several

sion. She had the security which she felt that she wanted most but which perhaps she needed least A brief summary follows·

"The general picture . . . is of someone at the mercy of her environment. She is apprehensive, lacking in self-assertion, and in constant need of reassurance. She suffers from feelings of inadequacy, is more *than ready to take more than her share of the 'blame' inherent in the* most trivial situations. She is someone who is probably easy to live with, just because she will adapt to the other person, on the general assumption that she is the one to submit. [In the history-taking her lack of aggressiveness and her submissive tendencies had been so *outstanding as to justify a comment concerning them.* She had remarked that she was a victim of circumstances, not aggression, but that she was not told what to do by her mother or husband—rather, that she went by their good example. She had added, thoughtfully, 'I probably am submissive but I have to be to keep peace.']

"Despite her (unsolicited) statement that she has an exceptionally happy marriage, it would appear that she lacks some aspects of instinctual satisfaction For example, the animals (the most explicit symbols for instinctual development) are seen as 'reaching after something,' i e unfulfilled. They are also 'leaning' and 'lying down'—very passive attitudes She is a passive person with a great capacity to take things lying down . . [During her history-taking she had said that her present marriage was *very* happy, that her husband was 20 years older than she, that they were well adjusted sexually, but that her experience in the past had been too terrible to allow her to think about sex, that she was contented but with no great passion, that her sex desire would be greater if she felt better but, as things were, she did not care In the past year she had been sick so much that "it might be six months" Before she was ill it had been "every few weeks" She "had no horror of the act but just not the desire"]

". . . because of her readiness to accept assistance and her reliance on authority, she is very likely to be helped by some supportive therapy. I do not feel that she has the stamina to profit by analysis That her personality picture contributes to the total picture I feel is unquestioned"

Figure drawings (Fig 43) were commented on by the psychologist as follows

"First of all, they show the same timidity, she is unable to use the

whole sheet of paper; just as in the Rorschach, she is content to use, and only feels safe with, the small detailed areas in the blots. She is a person who has definitely circumscribed activities, somewhat stiff,

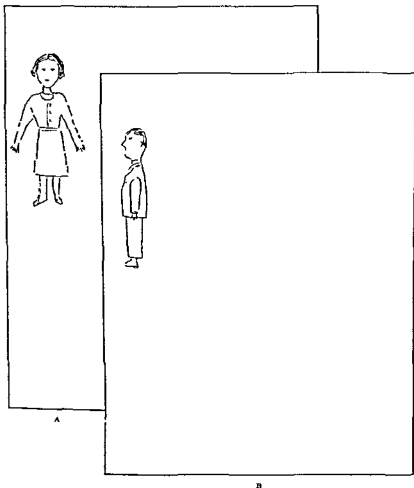


Fig 43 A and B Figure drawings See description in text.

and lacking in spontaneity. She does not dare to be spontaneous because that might incur disapproval She wants to be correct and to do the right thing. In speaking of her drawings she remarked several

times that she only wanted to draw outlines; she is afraid to show herself in any intimate way."

Analysis of expressive movements in handwriting was made by a second psychologist who did not see the patient and who had no knowledge of her, nor of the Rorschach findings:

"The writing has a somewhat dimmed character in its stroke, reflecting insecurity of judgment. . . . She is in many ways constricted She is overcontrolled, the portion of her emotions which passes her censorship is expressed in a mechanized kind of friendliness and good manners. . . .

"She is a very dependent person who leans on people, on a few only—and needs their constant approval. Along with this, she needs the feeling of being independent and the reassurance of being a personality. She has very marked feelings of inferiority. . . .

"She is submissive but her inferiority feeling prompts her to behave with persistence and not to yield. This is not easy for her because there is a longing for rest in her. She is tired Her tiredness may look like depression, but it is not real depression. If it were not for her inertia, she would be a woman of very good, practical abilities, with a flair for the solution of actual problems and with very good taste. However, she is given to reverie, to recurring thoughts, to memories

"She is an intelligent woman of good educational training, who has lost her flexible control and reacts now either in emotional complaintiveness or in an overcontrolled, masking manner"

This patient improved only moderately and temporarily under medical care which was combined with reassurance and attempts to bring about more fruitful use of her large amount of free time However, profound fatigue recurred with any slight physical or psychic trauma. She evinced interest in the psychologic study but evaded all early efforts to get her under the care of a psychiatrist. Later it was learned that she had been given to the compulsive use of alcohol and barbituric acid compounds periodically. Ultimately she accepted psychotherapy in a sanatorium

Case number eleven illustrates an immature behavior pattern in a patient with brucellosis, the concomitant psychoneurosis,

clinically evident and borne out by Rorschach and figure drawings, was of greater importance but difficult of management.

This 35-year-old married woman, mother of 3 children, had a history of three years of illness, originally attributable to brucellosis When first seen, residual complaints were headache, backache, excessive fatigue, and low-grade fever Further study left the question of active chronic brucellosis still unsettled Psychologically there was adequate reason for persistence of symptoms and avoidance of responsibility. During one interview she had said that she was physically unable to resume social and household responsibilities, adding, "And I don't see why I should try to do the things I don't care to do" She could not recall having made that statement, she was sure that she had said "things I am unable to do."

Psychologic study showed severe emotional problems, with evidence of anxiety, depression, and hypochondriasis, and poorly handled aggression, hostility and contempt, apparently aimed at the husband Immature reaction patterns were evident throughout

The figure drawings (Fig. 44) give further evidence of her conception of her husband and of herself—the male (probably husband) is puffed up to more than normal size while the female is a nice, sensitive, little girl (but with quite aggressive hands) In her drawing of the man, skillfully executed with adequate detail, the eye is conspicuously missing (Eye was mentioned recurrently in the Rorschach) The psychologist offered the guess that (1) she thinks of her husband as blind, (2) that she feels watched, on guard, and (3) that she blinds herself to the truth of her feelings about her husband (possible alternatives but probably simultaneously operative).

The patient did poorly under treatment Psychotherapy was to be undertaken but had to be deferred because of an abortive suicidal attempt. More than a year later, the husband, a physician, agreed to have a psychologic study made by the same psychologist, with the thought that he too might have psychotherapy. It seemed probable that the problem lay with the wife but that his cooperation would furnish an example or a challenge to her His study may be summarized as follows "An essentially introversial, submissive, passive, 'nice' individual, with apparently quite thin compensations in the direction of sociability and aggression Ego-strength is good, with some focus on work as a mode of adaptation. He had no positive

times that she only wanted to draw outlines, she is afraid to show herself in any intimate way."

Analysis of expressive movements in handwriting was made by a second psychologist who did not see the patient and who had no knowledge of her, nor of the Rorschach findings:

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"She is submissive but her inferiority feeling prompts her to behave with persistence and not to yield. This is not easy for her because there is a longing for rest in her. She is tired. Her tiredness may look like depression, but it is not real depression. If it were not for her inertia, she would be a woman of very good, practical abilities, with a flair for the solution of actual problems and with very good taste However, she is given to reverie, to recurring thoughts, to memories

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This patient improved only moderately and temporarily under medical care which was combined with reassurance and attempts to bring about more fruitful use of her large amount of free time. However, profound fatigue recurred with any slight physical or psychic trauma She evinced interest in the psychologic study but evaded all early efforts to get her under the care of a psychiatrist. Later it was learned that she had been given to the compulsive use of alcohol and barbituric acid compounds periodically. Ultimately she accepted psychotherapy in a sanatorium

Case number eleven illustrates an immature behavior pattern in a patient with brucellosis, the concomitant psychoneurosis,

pattern for handling aggression or coldness Instead he drifts along, with longings for magical relief from conflict While relief takes the form of death [in the thematic apperception test], I do not think there are active trends toward violence On the contrary, the death fantasies seem to represent merely a passive desire for release, and his main solution is adaptation 'at a slightly depressed level,' tailoring *his desires to his cloth as well as may be With more support he could* be himself happier and more genuinely strong"

The psychologist commented that the husband's problems apparently were relatively innocuous, that probably he could get along well with reasonable support, and even without it that he could survive, with emphasis on his work She stated "Of the two I think the wife would be the one for intensive therapy. If she can learn to tolerate her husband more or less 'as is,' *he* would probably improve also, so she would have less to tolerate objectively. If he had more *real* support from her, he would not have to compensate so much. The very thinness of test indications for over-compensation suggests that, even if clinically impressive, it could easily be renounced—far more easily than the deeper dependency needs"

A summary of the problem was presented to the husband and wife The wife agreed to have psychiatric treatment. Using brief methods, on a superficial level, improvement was notable

Results of Study

No attempt has been made to give a statistical survey. It is hoped that the general impression is reasonably clear—that use of psychologic methods of investigation often will supplement clinical and laboratory studies in patients presenting problems in either the somatic or psychic category, helping to distinguish between them and to evaluate either component when they coexist Specifically it is felt that the following theses have been supported.

1. that psychologic problems may be precipitated or intensified by chronic brucellosis,

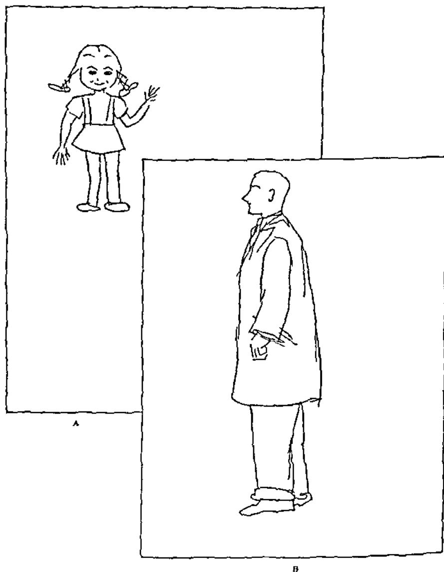


Fig 44 A and B Figure drawings See description in text

constant work and responsibility with no opportunity for more than a week-end away from it, pain, tenderness, and some apparent swelling developed at the site of an appendectomy scar and became steadily worse A ventral hernia seemed to be the logical explanation and operation was vaguely planned, whenever the load of serious illness among patients might allow. However, a surgeon found no evidence of hernia The symptoms disappeared and did not recur. With the realization that no longer was there a chance of an enforced period of idleness, the patient realized that it would have furnished welcome respite from responsibility, even at the expense of the discomfort incident to surgery. He had failed to take the course of action which would have shown greater maturity. Instead of informing his patients that he would be away on a much-needed vacation, he developed symptoms of illness requiring a period of idleness

Such an illustration has often served to explain various aspects of a neurosis, its cause, and its unusually simple means of cure. It also has to be explained that but rarely can anyone (even a physician) so readily dissipate a neurotic mechanism, that usually they are more deep-seated and more difficult to uncover.

Patients with chronic brucellosis are likely to be introspective, regardless of the degree and type of neurotic components, and to desire very full information as to results of tests. Obviously a Rorschach report may not be handed to any patient for his perusal, because of the implications present in so many and because of inability to understand its content, even if simply expressed. It can be explained in advance that the result will be couched in terminology which would be far beyond even the untrained physician's ability to interpret but that the general import and practical significance of the test will be explained to them.

It is the feeling of some psychiatrists that nothing can be gained from projective or nonprojective personality tests that cannot be elicited in psychiatric case-history taking and during psychotherapeutic sessions Even if this is true, much valuable material can be obtained *rapidly* by these methods—material that might require weeks to months to elicit through interviews alone

2. that psychoneurosis may simulate brucellosis, leading to fruitless treatment;
3. that chronic brucellosis may be masked by concomitant psychoneurosis, and conversely;
4. that psychoneurosis may interfere with recovery from the somatic illness;
5. that successful management of the physical illness may allow of better adjustment to previously existing emotional problems, and that the converse may be true.

It is usually not difficult for the patient to accept the theory that physical illness may be affected to some degree by emotional states and personality problems. It is, however, extremely difficult to gain acceptance by the patient that emotional conflicts may be important causal factors. The term "imaginary" has been used too long by physicians and laymen to characterize psychogenic symptoms, for patients to think in any other terms. The term implies to patients a state for which they are to blame—that they could "snap out of it" if only they chose to do so It seems of some value to tell patients that there should be no occasion for embarrassment about possible psychoneurotic components of their illnesses, that emotional problems of varying degree and importance exist in everyone, that it would be surprising if there were not such symptoms complicating a somatic illness of long duration, that even if the entire illness were psychogenic there would be no reason for shame—that it would simply mean a different approach in treatment

Nevertheless, patients are likely to consider that some stigma attaches because neuroses often are connected with "mental weakness," with malingering, or even with psychosis in the layman's mind. Success of psychotherapy, or indeed of getting patients under the care of psychiatrists initially, depends to a large degree upon their understanding and willingness to cooperate

In an attempt to explain the mechanism of neurotic reaction it has been helpful to relate a physician's experience with a manifestation of conversion-hysteria as follows. After several years of

mary" is used by physicians, then one cannot wonder that patients refuse to accept the concept of neurosis which is offered them, i e that neurosis may produce very real symptoms over which the patient has no control until their mechanism becomes clear to him, and that in no sense is he to blame)

"Chronic disease, then, is a psychosomatic problem which can only be understood if the pre-morbid personality with its influence upon the choice and course of disease is considered In addition, the pathological processes and its treatment might have psychological implications for the individual which, in turn, may influence the disease favorably or unfavorably In the latter case, a vicious circle is established, which leads to physical and psychological invalidism"

Ruesch well described the situation often encountered in the diagnosis and treatment of brucellosis and coexisting psychoneurosis

"Psychogenic symptoms if treated by medical and surgical procedures may finally become a physical problem Knowing this, the physician frequently finds himself in a dilemma. On the one hand, he feels compelled to rule out severe physical and organic lesions, on the other hand, he does exactly what neurotic patients want him to do He acknowledges the presence of physical ailments by his diagnostic procedures and diverts his attention from the psychological to the physical problems of the patients . . . The presence of anatomical or physiological changes does not exclude personality problems. The physician has to be trained in such a manner that he will be able to distinguish between frequently occurring psychogenic symptoms and other diseases, thus considering the patient in his psychosomatic entirety."

"In a great many instances, the investigator is confronted with a constellation in which the patient suffers from a severe physical disease on the one hand and has psychological problems on the other hand Immediately the question arises whether or not these findings are causally related Did the psychologic problems cause the physical findings, or did the physical pathology bring about, or possibly accentuate, the psychological problems? Or, did the physical and psychological problem develop independently from one another and merely influence each other later on, or are they an expression of a common cause, as in brain disease, for instance?"

In discussing the "perpetually referred patient," Ruesch stated.

In some instances the data would not be available at all because of the lack of opportunity for psychotherapy. In others psychotherapy would not be undertaken because of lack of apparent indications for it. Also, it is well known that patients may mislead a psychiatrist, consciously or unconsciously, for long periods of time.

ADDENDA

Since these observations were made a study entitled Chronic Disease and Psychological Invalidism: A Psychosomatic Study [77] has been published by Ruesch in collaboration with others. The conclusions drawn are heavily weighted from the psychiatric viewpoint. Chronic brucellosis was not included among the chronic diseases studied

In the foreword Bowman stated: "Patients equally ill from the same disease react quite differently. Some recover rapidly, while others remain more or less invalids indefinitely. The personality of the patient and the culture in which he lives are therefore thought to be important factors determining the outcome of the illness. It is recognized that while many patients desire quick and complete recovery, others find that continuation of symptoms may be a satisfactory way to dominate or punish others to gain prestige, to evade unpleasant duties, to obtain compensation or to achieve some other desired goal." Bowman unquestionably intended it to be understood that these reactions are on an unconscious level

In the introductory remarks Ruesch stated "The same personality factors which lead or predispose to a morbid condition are also present during convalescence Thus it becomes obvious that concurrence of psychological invalidism of any kind with chronic disease may prolong or postpone recovery indefinitely."

Other observations which have a bearing on the psychosomatic study of brucellosis follow "Complaints and symptoms, however, are in part the result of the individual's deliberate selection and reenforcement of peripheral stimuli What makes an individual suffer is determined by the manner in which he perceives his real or imaginary disease and not by the magnitude of the objective, pathological findings" (Selection of the term "imaginary' in contradistinction to "real" disease seems unfortunate It is important to avoid the use of this term in connection with psychogenic manifestations. If the term "imag-

Chapter VIII

PROGNOSIS

BRUCELLOSIS may not be considered a self-limited disease. The great majority of patients with acute brucellosis survive, but an unknown percentage fail to recover completely and are subject to repeated relapses of greater or lesser severity. The chronic phase may continue indefinitely or remissions and exacerbations may alternate throughout the patient's lifetime. Some apparent exacerbations may be due to reinfection, as in farmers, veterinarians, laboratory workers, and persons who persist in using raw milk and other dairy products. Resensitization from contact may produce symptoms of allergic origin which may be mistaken for reinfection or exacerbation, the infection itself apparently remaining latent in some and recurrent in others.

It is impossible to determine what percentage of patients make spontaneous recoveries, particularly since only a small fraction of infected patients are seen by physicians and their illnesses correctly diagnosed Whether or not recovery is complete and permanent, or whether all patients once infected continue to harbor the organism, is still uncertain. The patient who remains free of symptoms considered to be referable to brucellosis may have symptoms attributed to other illness which are unrecognized manifestations of *Brucella* infection

A patient once infected must be considered as potentially always infected If this is lost sight of, recurrences in the possibly distant future are not likely to be recognized. A history of brucellosis in the past often is ignored on the theory that the disease,

"Patients come to the doctor in order to be treated. Few come because they want to get well. They want to be treated for many reasons· some merely wish to talk with an educated man; some want to have reassurance to alleviate anxiety and fears; some like the authority of the physician and the glamor of medicine; some have hysterical symptoms and others suffer from over-concern with health" (Exception must be taken to this statement that "few come because they want to get well." In chronic brucellosis, with or without significant neurosis, it seems more likely that the patient seeks advice from one physician after another either because the total illness is not recognized or because it is not successfully treated In a number of patients it was evident that the patient clung to symptoms originally initiated by brucellosis itself because of psychologic problems which themselves were initiated or aggravated during the illness and which persisted It seems illogical to imply that they do not want to get well, *on a conscious level.* If a diagnosis explains why they are ill, in either the psychic or somatic category or in both, and if feasible means of recovery are offered them which they can accept, few patients will choose ill health. The greatest difficulty lies in allowing the psychoneurotic patient to see why ill health unconsciously is chosen)

Chapter VIII

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A patient once infected must be considered as potentially always infected. If this is lost sight of, recurrences in the possibly distant future are not likely to be recognized A history of brucellosis in the past often is ignored on the theory that the disease,

like typhoid, is self-limited, the error perhaps only coming to light through isolation of the organism.

In many patients the persistence of a high phagocytic index, in the absence of clinical symptoms referable to brucellosis, following vaccine therapy, has furnished an excellent prognostic sign Patients have been observed in whom phagocytic activity from moderate to high degree has been maintained for ten years or more (p. 458). However, it is not certain that these patients have completely recovered and are fortunate in remaining relatively immune to reinfection or whether their relative immunity is maintained by virtue of continued subclinical infection.

Relapse and Reinfection

The farm laborer whose protracted acute brucellosis is described on page 166, gave a history indicating a chronic *Brucella* infection for nine years preceding the acute exacerbation. Following remission of the acute illness, *Brucella* vaccine was given in an attempt to overcome the chronic illness and to prevent relapse of the acute process. He was discharged symptomless and apparently recovered. He remained well for four years, working steadily as a laborer on a dairy farm At the end of that time he returned complaining of severe left-sided chest pain, fatigue, headache, backache, and orchitis In trying to decide whether this patient had become reinfected in the course of his employment or whether he had never completely recovered, it was established that he had not been free of backache at any time. Whether or not he also had had low-grade fever and other symptoms not likely to become evident in one of his phlegmatic temperament could not be determined He again responded to *Brucella* vaccine therapy but the future course of the disease remained unpredictable. This patient's illness, like many others, can be classified as recovery or cure followed by reinfection, or as one with remissions and exacerbations over a fourteen-year period, depending upon the viewpoint of the statistician. Often patients are said to have recovered as soon as remission in symptoms occurs.

It is probable that reinfection may result in intensification of *existing symptoms or in an entirely different syndrome.* A farmer's wife, previously apparently well following treatment of a protracted subacute illness, had two further attacks, differing in localized manifestations, which were ascribed to relapse. Later she recalled that her husband's herd had been swept by contagious abortion on three occasions, in each instance just prior to her own acute attacks. The husband of this patient gave a history suggesting that his infection dated back nearly twenty years. Vaccine therapy failed to bring about more than temporary improvement It is quite conceivable that he too was repeatedly infected, especially since his work kept him in frequent contact with infected cows and stillborn calves. No similar experience has occurred in those not exposed repeatedly. Lighting up of latent infection through allergic reaction to subsequent exposure may play an important role

Evidence that reinfection is possible was furnished in the reports of Jordan and Borts [383] of double infection with *abortus* and *melitensis* species in one patient and of Hardy, Jordan, and Borts [294] of isolation of both the *abortus* and *suis* species in another patient. In the former case epidemiologic study indicated that the Mexican railroad laborer had acquired the *melitensis* variety of infection in Mexico and the *abortus* variety subsequently in Iowa. It is unlikely that infection with two varieties were contracted simultaneously.

Duration

If untreated, the duration of the acute or chronic illness is unpredictable, nor can the likelihood or the number of relapses be estimated. Although a persistently high phagocytic index after apparent complete clinical recovery usually is of favorable significance, death can occur in the presence of the highest measurable phagocytic activity (p 329). Negative cultures in patients who have previously had positive cultures cannot be used as a criterion of cure. The organism may still be present in various foci, active

or quiescent, and perhaps growing intracellularly. Hughes[662] found the average pyrexial period in 372 patients to be fifty-eight days, but he estimated it to be from sixty to seventy days if unnoted relapses were considered. Two of his patients had fever for two years; he quoted Veale as noting fever of two years duration and Bruce one of eighteen months duration. In all probability the fallacy that brucellosis always "burns itself out" in eighteen to twenty-four months, as quoted so frequently, derives from these early observations. The average time in hospital of 844 cases was from seventy to ninety days. As for complete recovery, Hughes wrote that it may take twelve to fourteen months, "while many seem to take years to shake off its effect." It is, of course, a question whether these patients were "shaking off" the effect of infection or the infection itself. Observation of the same patients over a period of ten or more years makes the latter concept much more acceptable. There seems little doubt that the duration of infection may be limited only by the life-span of the individual.

Childhood Infection

In general the prognosis in children as to complete and permanent recovery is excellent, although not necessarily as uniformly so as previously reported.[490] In 2 children, aged 8 and 14, previously treated with vaccine, recurrence of symptoms became evident several years after they were dismissed as apparently cured. The question of reinfection was open, both had had raw milk at times since vaccine therapy was concluded. In a third patient, first treated with apparent complete success at the age of 14, relapse (or reinfection) occurred nine years later.

Children whose infections have apparently been obtained through the ingestion of milk seem to have a better prognosis than those in whom infection was probably transmitted by the mother, according to Hagebusch and Frei.[285] There were 11 spontaneous recoveries in those presumably infected by milk or milk products and none in those presumably infected by the mother. They noted that the course was milder in the former group. After

waiting as long as eighteen months for recovery in the latter group, vaccine therapy was employed.

Borts[71] commented that children, for the most part, tolerate brucellosis much better than do adults He mentioned 3 subclinical cases in school children occurring among an outbreak of brucellosis in Iowa in 1943 *Brucella suis* was isolated from the blood stream and agglutinins were present in the blood in high titers Aside from anemia and a little lassitude, these children were otherwise normal, they did not miss a day of school It would be dangerous to base any prognosis on the freedom from symptoms then existing, however, since exacerbation may be so rapid and unheralded.

Mortality

Hughes[369] stated, in 1897, that the mortality of brucellosis was about 2 per cent. This figure has been quoted by most contributors to the literature since, without regard to acuteness or chronicity of the illnesses under consideration. Hughes' cases were largely of the acute variety and infected with the virulent *melitensis* species of *Brucella* Among approximately 600 cases in the author's series, the vast majority of which were chronic, only one death directly attributable to brucellosis occurred This was in a chronic illness with central–nervous-system involvement.[303] No specific therapy was attempted, the diagnosis not having been proved by culture Many of the acute cases occurred before the advent of the sulfonamides or of streptomycin Two of these early cases were desperately ill and might have died If any mortality had occurred it might well have been preventable had bacteriostatic or bactericidal drugs been available. There were 3 per cent of deaths in the series of 375 patients reported on by Hardy and his coworkers[294] in 1931 They stated that *suis* infections are more virulent and that good prognosis usually could be attributed to cases of *abortus* infection Undoubtedly present-day methods can reduce mortality markedly, even in the most severe infections.

Epidemic milk-borne *Brucella* infection results in very variable mortality rates Farber and Matthews[209] in 1929 reported an out-

break of 26 cases of *abortus* infection in Indiana with no deaths; Beattie and Rice [46] in 1934 reported an epidemic of 30 cases of *Brucella suis* infection in Iowa with no deaths; Horning [342] in 1935 reported an outbreak of 14 cases of *Brucella suis* infections among elderly patients in Connecticut with 3 deaths (21.4 per cent); Borts, Harris, Joynt, Jennings, and Jordan [74] in 1943 reported 77 cases of *Brucella suis* infection in Iowa with no deaths. Sharp [620] erroneously quoted an outbreak in France of 160 cases among 630 inhabitants with 40 deaths (25 per cent), the original article stated that a Paris newspaper had quoted a deathrate of 40 among 106 cases but an investigation by Aubert, Cantaloube, and Thibault [80] showed that the outbreak was disseminated, with a mortality of about 7 per cent (p. 88).

Angelini [18] reported the mortality from brucellosis (which is endemic in Mexico City) as 9.8 per cent, "much higher than that which is usually indicated in standard books on the subject." He attributed the high mortality rate largely to poverty, with a tendency to poor hygiene and food. The fact that the majority of cases in Mexico are due to virulent *melitensis* strains is undoubtedly also a factor.

A mortality of 35 per cent was said to have occurred in one province of Argentina (Mazza).[465]

In the ten years from 1932 to 1941, 26,575 cases were reported in the United States, with 910 deaths (3.4 per cent). As stated elsewhere, since the disease itself is relatively rarely diagnosed in proportion to its true incidence and since severe acute infections are the only ones likely to be diagnosed and reported, true mortality figures are likely to be lower than the percentage quoted.

Mortality depends in some degree upon the localization of infection. It is to be expected that involvement of the central nervous system, the heart, liver, or kidneys would produce greater mortality than less vital localization

Central-nervous-system localizations are serious but not necessarily fatal. Many proved cases of central-nervous-system involve-

ment run a relatively benign course or are susceptible to various forms of treatment (p 236). Of the 11 verified cases reviewed by DeJong,[168] 3 terminated fatally, 6 recovered, and 2, including his own case, remained more or less stationary. The number of cases was too small to be of value in relating prognosis to the variety of *Brucella* involved

Two cases of *Brucella abortus* meningitis reported by Poston and Smith[540] and Poston and Thomason[541] (p 242) recovered following specific therapy. There was a fatal outcome in 11 of the 12 other cases occurring in children, the one who survived later developing a transverse myelitis. The gravely ill patient described by the author on p 238 recovered, apparently in response to sulfadiazine Another recovered apparently by virtue of *Brucella* antigens The patient reported by Roger, Pieri, and Bouet[585] (p. 241) recovered after repeated attacks The case of meningo-encephalitis due to the *suis* variety reported by Sanders[593] and by Hansmann and Schenken[298] (p 242) ended fatally through rupture of a mycotic aneurysm of the basilar artery. The patient with extensive metastatic *Brucella abortus* encephalitis reported by Scheiddeger and Stern[602] ended fatally. The patient with *Bru-* [illegible] illice, and Jordan[313] [illegible] Three patients seen [illegible] dence of low-grade encephalitis, recovered under treatment with a bacterial antigen complex, one relapsed and was treated with streptomycin and sulfadiazine, with recovery.

The actual mortality of *Brucella* infection of the central nervous system can only be estimated rather than accurately computed since the etiology in many cases reported in this category (including the 6 described by the author) was not established by culture and because many cases undoubtedly due to *Brucella* infection are not recognized as such (see discussion of differential diagnosis, page 358) It seems probable that the mortality varies with the species (and perhaps the strain) of organism, the age and general condition of the patient, and the stage of the illness at which treatment was instituted.

The outlook in cardiovascular involvement due to *Brucella* (mycotic aneurysm, myocarditis, pericarditis, or endocarditis) apparently is grave although it is probable that this too can be altered by early recognition and suitable therapy. Hughes and many other observers (p. 99) have reported almost uniformly fatal results in pericarditis and endocarditis of *Brucella* origin. The few cases of mycotic aneurysm reported ended fatally. The mortality from thrombophlebitis due to *Brucella* infection (p 176) cannot be evaluated since few cases have been reported but many cases, in all probability, are not recognized. No case of *Brucella* endocarditis has survived, apparently, although it may be expected that employment of streptomycin and sulfadiazine concomitantly, or other antibiotic, could alter this outlook

Hemorrhage in the alimentary tract may alter mortality statistics in brucellosis if the etiology is recognized (pp. 114 and 116).

Liver disease due to *Brucella* infection has only recently come under consideration It is too early to say to what degree it may contribute to mortality (pp. 109–114).

Nephritis complicating brucellosis may contribute toward death, judging from the severity of an acute nephritis occurring in one of the author's patients (who recovered). This view is supported by one case of chronic nephritis (who also recovered), and the case reported by DeGowin, Carter, and Borts [165] who died of *Brucella suis* endocarditis, nephritis, and rupture of a mycotic aneurysm (pp 117 and 188). As in other manifestations of brucellosis, the diagnosis may have been made in only a small percentage of cases.

Without a virtually impossible follow-up, no statistics as to mortality can be reported with accuracy. Tables IX, X and XI show the officially recorded deaths in the United States and in those other countries where any reports, however incomplete, have been made It is also impossible to evaluate the indirect mortality of *Brucella* infection, since it may not lend itself to proof at autopsy even if the disease were suspected as being a contributory factor before death

TABLE IX

CASES AND DEATHS AND CASE RATE AND DEATH RATE PER MILLION OF POPULATION FOR THE TOTAL UNITED STATES REPORTED BY STATES *

1943–1947

	1943		*1944*		*1945*		*1946*		*1947*	
	Cases	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*
Number	3734	77	4436	80	5049	94	5687	69	6147	†
Rate per million population	27 9	0 6	33 5	0 6	38 2	0 7	40 7	0 5	42 9	†

* Source United States Public Health Service, National Office of Vital Statistics

Discrepancies exist between morbidity as well as mortality figures issued by Public Health Reports (*Notifiable Diseases*) and by the National Office of Vital Statistics because of the manner of reporting (some reports are preliminary), corrections, and delayed reports

† Figures not available

TABLE X

DEATHS AND DEATH RATES PER MILLION POPULATION FROM UNDULANT FEVER, BY AGE, RACE, AND SEX, UNITED STATES 1940–1945 *

		Deaths					*Death Rates*			
Age Group	*Total*	*White*		*Colored*		*Total*	*White*		*Colored*	
		M	*F*	*M*	*F*		*M*	*F*	*M*	*F*
All ages	506	289	164	34	19	0 6	0 8	0 5	0 8	0 4
Under 15	29	11	13	3	2	0 1	0 1	0 1	0 2	0 2
15 to 24	44	24	15	4	1	0 3	0 4	0 2	0 6	0 1
25 to 34	66	34	18	10	4	0 5	0 7	0 3	1 7	0 5
35 to 44	68	43	19	3	3	0 6	0 9	0 4	0 5	0 5
45 to 54	92	54	23	11	4	1 0	1 2	0 5	2 7	1 0
55 to 64	94	66	25	1	2	1 4	2 1	0 8	0 4	0 9
65 to 74	77	41	33	1	2	1 9	2 2	1 7	0 7	1 6
75 and over	36	16	18	1	1	2 1	4 4	2 1	1 3	1 6

* Source National Office of Vital Statistics, United States Public Health Service

TABLE XI

DEATHS FROM BRUCELLOSIS REPORTED FROM VARIOUS COUNTRIES, 1936–1947 *

Country	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
AFRICA												
Egypt	1	8	14	3	2	0	2	4	3	2	0	0
Anglo-Egyptian Sudan	4	1	3	1	2	3	1		3	2		..
Kenya					0	1	0	0	0	1		.
AMERICA												
Bermuda				0	1		0	0	0	.		
Bolivia										12	3	.
Canada	8	11	14	8	9	4	8	4	5		.	..
Chile				1	0	1	1	2	7		.	
Mexico				139	194	198	206	222	203	259	252	130
Peru									92	75	.	
United States °	115	93	118	121	116	71	79	98	82	101	69	
ASIA												
Palestine					0	0	1	0	0	0		..
Iraq					2		0	0	0	0	0	0
EUROPE												
Germany	15		19	4	8	9	1	2	.	.	1	5
Austria					1	1	0	1		0	0	0
England and Wales	4	10	12	6	4	7	6	1	7	3		...
Scotland	1	1	2	2	0	0	4	1	0	0		
Denmark	12	11	18	4	6	6	6	6	1	2	1	..
Estonia	1	0	0								.	
Finland	3	0	3	3	1					.		
France					.			.		84	70	.

Greece	16[b]	30[b]	24[b]	1	0	0	0	0	0	1	0	1
Hungary	0	1	0									
Ireland				2	0	1	2	1	0	1	1	0
Italy	186	220	183	219	187	178	183					
Malta and Gozo	52	60	50	52	38	31	16	9	8	26	39	32
Netherlands				1	0	0	0	1	1		2	1
Norway				0	0	0						
Poland	1	1	0									
Spain					110	110	97	41	120	148	71	91
Sweden	1	7	9	3	1	0	2	1	0			
Switzerland	6	1	5	5	6	7	5	8	5			.
Turkey	0	1	0	0	1	0	0	0	0	0	0	1
OCEANIA												
Australia							0	1	0	0		
Hawaii				0	0	0	0	0	0	0		
New Zealand				2	1	0	0	0			.	
YEARLY TOTALS, ALL COUNTRIES REPORTING	426	256	474	577	690	627	620	403	537	717	515	261

[a] Compiled from data supplied by United Nations, World Health Organization, Interim Commission, Division of Epidemiology and Public Health Statistics, through the courtesy of Dr. M. Cakrtova, Medical Officer (based on incomplete statistics)

These figures do not represent the actual but rather the reported number of deaths Only deaths in obvious, culturally proved cases are likely to be ascribed to brucellosis Many countries have rendered no reports or only occasional ones Others have ceased reporting because of postwar conditions (e g , no figures are available for Russia or Eastern European countries)

[a] Discrepancies exist in these and other figures compiled from World Health Organization data as compared with United States Public Health Service statistics because of the manner of compiling

[b] Mortality, morbidity ratio for the years 1936–1938 (16 23, 30.54, 24.69) are extremely high, probably due to incomplete reporting of morbidity figures

Chapter IX

TREATMENT

General Considerations

EVEN before the advent of antibiotics the management of acute and chronic brucellosis had made great progress. Through use of the sulfonamide compounds the acute illness could often be terminated and, through subsequent use of effective *Brucella* antigens, relapse usually prevented. In the chronic illness the most effective treatment, in the opinion of the majority of those who had observed large numbers of patients, was based on one or another form of specific *Brucella* antigen.

There had, however, persisted a defeatist viewpoint in the minds of many.[204] Recently there has been evidence of a reversal of this view, attended by overenthusiasm for antibiotic therapy, sometimes without due regard to possible adverse effects.

As is usually true, the moderate course of action seems to be the best—to retain what is tried and proved of the old and to add, with caution, that which gives promise of the new. Each patient furnishes an individual problem. In some it may be an extremely difficult one.

Supportive measures have become less necessary. When indicated they differ in no important respect from other illness.

Fever in the acute illness may require special measures until the infection can be controlled. Reports of extreme hyperpyrexia with fever beyond 108° F. rectal are usually considered to be evidence of malingering but the occasional occurrences of extreme fevers in unconscious, near-moribund patients (p. 157) with

recovery, make it necessary to be prepared for their management. The height of fever may indicate central–nervous-system involvement and thus suggest changes in therapy. In the chronic illness fever need only be considered as one manifestation of the infection; rarely is it of concern in itself.

Perspiration requires the usual type of management, seldom requiring administration of atropine or similar drugs.

Elimination needs no special attention except awareness that nephritis may develop and that constipation may be severe. Intravenous fluids are of value in the acute illness in the presence of vomiting Although protein requirements are high, caution in the intravenous administration of protein hydrolysates is suggested unless the indication is clear-cut. One instance of apparent sensitivity to a protein hydrolysate was noted, [311] the nearly fatal outcome of the reaction, which was of the nature of atypical protein shock, made the procedure seem of questionable wisdom

Diet should consist of a high protein, high carbohydrate, and low fat intake. The liver-protection and nutritive value of protein seems to be especially important in the acute or chronic illness, especially in the presence of hepatitis

The vitamin content of the diet is of importance in the acute or chronic illness if natural dietary sources are inadequate. Vitamin B complex may have special virtue in stimulating phagocytosis. The early concept that vitamin C also has value in combating infection has received recent further support.[12] The parenteral use of both B complex and ascorbic acid may be indicated when there is vomiting or intolerance, with due consideration of possible sensitivity to some components of the vitamin B complex.

Rest in bed in the acute pyrexial stage is essential. Borts [13] stated that a fair share of the complications and development of the chronic phase can be prevented if there is recognition of early cases and early treatment He favored bed-rest for a minimum of two weeks after temperature had become normal or subnormal. In some patients this cannot be achieved, in spite of otherwise successful methods of treatment, low-grade fever persisting indefi-

nitely. Indefinite prolongation of bed-rest may be useless and even harmful.

Rest in bed as a therapeutic agent in chronic brucellosis has been advocated by many, on theoretic or practical grounds Its efficacy has never been sufficiently demonstrated to justify the prolonged periods of idleness, unproductivity, economic loss, and the increased frustration which is so often induced. Many patients who had devoted from several months to several years to complete rest, at great financial and emotional sacrifice, failed to register sufficiently significant improvement to justify the method. Prolonged periods of rest were an integral part of naval hospital procedure, little or nothing seemed to be accomplished in any of 30 instances directly or indirectly known to the author. In those cases reported by others in whom recovery followed prolonged bed-rest, it is quite possible that rest played a relatively unimportant role and that recovery would have been equally as prompt with a less intensive rest regime.

That undue fatigue can have a deleterious effect can hardly be doubted The personality of the patient, the severity of the illness, and the apparent effect of previous periods of rest or undue activity should be assessed before definite advice is given. In a very few patients in whom rest regimens were initiated of their own volition or by force of circumstances, marked clinical and serologic improvement was noted, however. It is axiomatic that adequate hours of sleep and freedom from undue stress, physical and emotional, are important.

Climatic influence on the course of the disease becomes less important as methods of treatment improve. That high, dry climates are of special value in the treatment of the chronic illness or of the prolonged acute illness has not been convincingly demonstrated Some patients have reported greater vigor and lessening of all subjective complaints while sojourning in the Swiss Alps or other high altitudes On the other hand other patients have found that humid climates, at sea level, have agreed with them equally as well, or better It requires great self-confidence on the part of the physician to advise radical changes in the patient's

way and place of living to bring about the hoped-for salutary effects of change in environment. What benefits may ensue may be psychogenic or coincidental.

Anemia is best treated from its incipiency since it may develop slowly and insidiously or rapidly and in profound degree, even in the chronic illness Its treatment is usually that of other secondary or nutritional anemias, with iron, crude liver, or liver fractions. If blood transfusions are indicated selection of the donor to include consideration of the donor's immune status is advisable (p 449).

Anemia in brucellosis is likely to be extremely refractory, in some instances yielding to average doses of ferrous sulphate or other forms of iron, in other instances apparently requiring liver fractions in addition to iron, orally or parenterally. Failure of response to one form of liver fraction or crude liver extract may be followed by ready response to another form of parenteral liver, or a liver and iron mixture orally, for no reason that is apparent.

Pregnancy requires careful consideration because of the possibility of abortion and because the common manifestations of pregnancy may aggravate, or be aggravated by, *Brucella* infection. Anemia in pregnancy requires special attention. Active treatment of the acute infection is essential, usually with carefully prescribed amounts of a sulfonamide compound, overlapped by reactionless doses of *Brucella* vaccine unless natural phagocytic response is adequate (p 431) In general, chronic brucellosis which is under therapeutic control, and with no evidence of involvement of the reproductive organs, is not a contraindication to pregnancy. It has seemed wise to administer reactionless doses of an effective *Brucella* antigen to pregnant patients if symptoms exist or have recently existed

Prenatal immunization may be accomplished as well as prevention of abortion, through administration of *Brucella* antigen, throughout pregnancy. No patients so treated aborted; however, no conclusions may be drawn from this Schmidt[607] presented some evidence that it may be successful.

Dental care has been stressed by the author [294, 299] and its importance recently emphasized by Martinez.[404] Eradication of gingival and apical foci of infection has seemed to exert an important influence.

Psychotherapy is discussed at length in Chapter VII, along with diagnosis of emotional states resulting from, antedating, or coexisting with brucellosis. Simple measures are employed routinely in the way of reassurance and often are of great importance Many patients are disheartened by long-continued or frequently recurring symptoms and the fact that they are often told that no treatment is likely to be of any avail. Optimism is justified as to the eventual outcome, while admitting that not all patients respond with the same promptness or completeness, and that the exact duration of the illness cannot be predicted. The public is still poorly informed about brucellosis in spite of the number of articles which have appeared in the press. Many of these articles are actually deliberately misleading because of the peculiar journalistic concept that the public will not read anything that is not spectacular.* Much fear can be dispelled in these patients by the truthful statement that the disease is common, that one or another method of treatment is almost certain to bring about recovery, if not actual cure, and that the likelihood of survival is almost 100 per cent

Medication

Thyroid medication is often misused in the presence of recent or remote or inadequate evidence of hypothyroidism. Not infre-

* For example, a conservatively written article, stating simple truths about brucellosis, was contributed by the author to a widely read magazine following its approval by the New York Academy of Medicine and with the permission of the Bureau of Medicine and Surgery of the Navy It had been stipulated that any editorial changes would have to be approved by the author In spite of this agreement, the article was rewritten in a manner that was objectionable to the extreme It contained exaggerations and unwarranted statements which then were deleted by the author These deletions were ignored and the article was published containing the material which the author had specifically forbidden The editor refused public retraction but admitted, in writing his responsibility for the changes made

quently patients have been seen for whom thyroid extract was prescribed several years before and who have continued the medication without further medical supervision

A 45-year-old woman had taken 12 gr. of thyroid extract daily for two years and then 5 gr. daily for the next two years before being referred for an opinion as to the existence of chronic brucellosis Her chief complaints were fatigue and tachycardia. Basal metabolic rates had been only moderately low at the time these excessive doses of thyroid extract were prescribed. The greater the fatigue that ensued the greater had been considered the need for thyroid medication The more weight she gained the more certainly had it been thought that thyroid medication was vital Her basal metabolic rate was found to be +50 while taking 5 gr daily, pulse rate was 120, at rest There was evidence of a low-grade *Brucella* infection However, more important than its immediate treatment was withdrawal of all thyroid medication Within four weeks after it was stopped pulse rate was normal, and fatigue and "jitteriness" markedly lessened

In several patients it was impossible to determine whether there had been true underactivity of the thyroid, or whether the thyroid extract had been given because of borderline basal-metabolism rates, tendency to slow pulse, and fatigue Such syndromes are often a part of the picture of chronic brucellosis Use of even moderate amounts of thyroid extract (as little as 2 gr. daily) in such situations apparently has been responsible for induction of thyroid intoxication Under most circumstances it seems proper to withhold prescription of thyroid medication until its need is fully established and then to supervise the patient for as long a time as its use seems indicated

Crude liver solution parenterally may be of value to stimulate hematopoiesis, and for its vitamin-B content and theoretic liver protective action in the absence of anemia.

Concentrated liver fractions may bring about greater reticulocyte response in some patients

Sedatives are not contraindicated in brucellosis but may be prescribed with the same judgment as in other acute or chronic illness.

Stimulants may be of value for temporary use. *Racemic amphetamine sulfate* (benzedrine) or *d-amphetamine sulfate* (dexedrine) or similar compounds may be of value in lessening depression and fatigue when used infrequently and in small amounts; their continued use in large dosage is to be discouraged. *Alcohol* in moderate amounts possesses apparent value; in amounts sufficient to produce intoxication, deleterious effects have been apparent in several patients with lowering of general resistance, apparently sufficient to cause repeated relapse or refractoriness to the usually effective treatment; phagocytosis may be depressed.

Physical Therapy

Arthritis, spondylitis, neuritis, pleuritic pain, unresolved pneumonia, cholecystitis, salpingitis, and various other manifestations of brucellosis may yield to a combination of physical procedures and specific measures when they fail to respond to any single method alone.[301] Feldman [212] recommended diathermy, roentgen rays, and ultraviolet light as important adjuncts to specific measures. Artificial-fever therapy has been stressed in varying degree by many observers.[197, 242, 393, 532, 545, 546, 632, 643, 737]

Izar and Moretti [374] used ultrashort waves (4- and 8-meter wavelengths) in treatment of the spleen alone or spleen and liver in 9 cases of *Brucella abortus* infection with "cure" in 6. Although the theory of selective biologic action of various ultrashort waves on certain organisms has not been widely accepted, the method described cannot be completely discredited, especially in view of the apparently excellent results achieved by the author in *Brucella* salpingitis using 6-meter wavelengths. It is possible that the effect produced is that of heat alone

Short-wave diathermy has proved particularly valuable in the treatment of *salpingitis.* The most effective method found employed the 6-meter wavelength, the Bierman or Gottesman vaginal electrode (with thermometer incorporated), and air-spaced indifferent electrode over the lower abdomen or beneath the treat-

ment table underlying the sacrum (or with alternation of the two applications). A long cuff electrode may be used as a partial belt at or just below the waist line. (Placement of the indifferent electrode directly beneath the sacrum, with the weight of the patient on it, results in too great a concentration of heat externally.) To initiate treatment, it is administered daily or at least three times weekly. Electrode temperatures ranging from 106 to 108° F. are obtained if within the limits of the patient's tolerance. The temperature recorded by the intraelectrode thermometer is that of the electrode and not necessarily that generated in the pelvic organs. It is, however, an essential guide to the milliamperage employed, along with the patient's sensation of heat, although neither is a sufficient guide by itself. The apprehensive patient may receive an ineffective degree of heat and the one overly anxious for results may endure more than can safely be given without burns. Duration of treatment has been from thirty to sixty minutes rather than the shorter periods frequently employed The total number of treatments may vary from one to several courses of from twelve to twenty treatments each The method described seems to result in greater localization of heat in the uterine adnexa than by other methods

This technic has been employed successfully in 15 patients with unilateral or bilateral salpingitis, presumably due to *Brucella* infection, who had failed to recover completely under *Brucella* vaccine therapy alone In no instance was salpingectomy necessary. Actual sterilization of foci may not be effected, relapse may occur, requiring repeated courses The individual case requires decision between such conservative measures and extirpation of the focus. Caution must be used in recommending surgery in known localized infections because of the possibility of other localizations which may result in continuation of the illness.

In joint involvement, cuff electrodes above and below the involved joint has been the preferred method, whenever applicable

In cholecystitis there has been apparent success in several patients Since the method has been used only in patients refractory to vaccine therapy alone and in conjunction with it, it is difficult

to assess the value of diathermy alone. Apparent restoration of normal gallbladder function as demonstrated by the Graham-Cole technic may have been due to improvement in liver function through increased circulation. It was particularly notable that clinical recovery followed when diathermy was added to the vaccine regimen.

In *unresolved pneumonia* and in the presence of *pleuritic pain*, the coil technic or the use of two pads is usually effective in hastening resolution.

In neuritis, of brachial or sciatic-nerve distribution, combination of cuff and pad technic is usually desirable.

Artificial fever may be induced by the various types of fever cabinets or by intravenous use of typhoid or typhoid-paratyphoid vaccine. Neither method can be said to be without danger, even in the most expert hands. The possibility of uncontrollable febrile reactions seems greater from the use of intravenous typhoid organisms than from the fever cabinet. Death from the former method may not be preventable, once the mechanism has been set in motion. Febrile response is subject to greater control in the use of the fever cabinet

Two attempts were made with the fever cabinet to treat a 28-year-old woman suffering from chronic brucellosis of long standing, by a physician of unsurpassed skill and experience in this field. The first treatment was preceded by morphine (1/6 gr.) hypodermically By the time temperature had reached 104° F. the patient became disoriented, apneic, and was removed from the *cabinet at the end of three hours in a state of imminent* collapse; disorientation lasted for several hours Seconal sodium preceded the second treatment three days later, with a similar near-collapse. The patient had shown no idiosyncrasy to morphine or to seconal sodium prior to or following this experience A psychic factor, involving fear of death, accentuated by the coffin-like appearance of the cabinet, may have been a contributing factor (pp. 238 and 377).

In 5 patients in the chronic phase treated by artificial fever by Spink and Hall [643] after failure of sulfonamide compounds, satisfactory results were attained in 4.

Many of the favorable results have been reported after short periods of observation. Fowlks[242] presented 4 cases in detail, in which the period of observation following treatment with intravenous typhoid vaccine was from a few months to a year. It is desirable that the method be evaluated after five years or more of observation.

Using the fever cabinet Simpson[632] gave 6 sessions of three hours duration, with rectal temperatures of 105° F., in a two-week period Phalen, Prickman, and Krusen[532] gave 3 sessions of five hours duration, with rectal temperatures of 105 to 106° F, at three-day intervals. Simpson advised use of the method in patients who proved refractory to vaccine therapy.

The favorable effects of fever therapy cannot be attributable to fever alone since *Brucella* is known to survive temperatures of 107° F. for twenty-four hours in vitro and since patients with extreme hyperpyrexia may fail to make spontaneous recoveries It is thought that activation or heightening of the protective mechanisms of the body may be brought about in some unexplained manner

Spondylitis seems to be the manifestation of brucellosis most likely to respond to artificial-fever therapy. The reparative processes which are likely to be induced naturally or with the use of *Brucella* vaccine apparently are hastened Lasting recovery from fever therapy alone can hardly be expected in more than a small percentage of patients.

Ultraviolet irradiation of blood using the Knott technic, was employed by Miley[469] in 2 cases of chronic *Brucella* infection, proved by culture Improvement was noted after six or eight months of treatment Treatment was given first at monthly intervals, as improvement began, intervals were lengthened to six or eight weeks One had been under observation for three years and one for five years, both receiving 3 to 5 treatments per year throughout that time and remaining well He considered that patients would require 8 to 12 treatments in the first ten to twelve months, followed by 4 to 6 irradiations in every succeeding twelve-month period Its curative value has not been proved.

Roentgen-ray treatment of the spleen or other suspected areas of localized infection has not been sufficiently evaluated Because of the apparently frequent localization of *Brucella* in the spleen, further experimental studies seem desirable.

Foreign protein therapy, particularly by means of intravenous typhoid vaccine, is favorably considered by many.[197, 460, 491] It was used by the author in a number of patients with temporary effect only in some, and with no apparent good effect in others. Some favorable effect from its use may occur since any fever producing agent may conceivably alter the course of the disease. Other forms of shock therapy through foreign protein injections, including intramuscular injections of sterile milk and bacterial proteins prepared from *Brucella*, have been reported in the early literature,[35, 214] with inconclusive results.

Ervin and Hunt [196] stated that most successful methods of treatment of brucellosis are accompanied by sharp thermal reactions, "whether the treatment given is administration of a vaccine, toxic filtrate, specific serum, chemical or foreign protein or fever induced by mechanical appliance" This concept is not supported by the evidence of many who have treated large numbers of patients and have observed them over long periods of time. Simpson [6-8] carried out control studies with typhoid vaccine and sterile milk injections in an effort to determine whether or not results from *Brucella* vaccine were ascribable to foreign protein effect; he found that the foreign proteins did not appreciably alter the course of the disease. Sharp thermal reactions have been avoided by the author in a large series of patients, with the conviction that they are neither necessary nor usually desirable. Rarely is chronic brucellosis so serious a disease as to justify the risk involved Specificity of *Brucella* vaccine therapy is discussed elsewhere (p 454) If fever-producing methods are indicated, because of the failure of *Brucella* vaccine, or the existence of contraindications to its use, artificial-fever therapy by means of a cabinet, administered by physicians and technicians expert in its use, seems preferable.

CHEMOTHERAPY

Mercurochrome, trypan blue, methyl violet, metaphen, chrysogenine, rivanol, acriflavine, methylene blue, gentian violet, and other chemical compounds intended for intravenous or oral use or by enema have received favorable mention in the literature but few reports included a sufficient number of patients observed for a long enough period of time Fortney[231] reported the apparent cure of one patient suffering from acute brucellosis after two doses of metaphen given intravenously; the report was made after only three months of observation. However, Abbott and his associates[3] reported its use with striking results in 10 acutely ill patients, in 1937. In a later personal communication Abbott[1] stated that the patients had been followed from three to eleven years with no evidence of return of the disease in any case. He[2] had been one of the 10 patients and had had no recurrence for more than nine years. In some 30 cases in subacute or chronic phases Abbott reported poor results, with "some improvement or cure in about 15 per cent"

Carpenter and Boak[170] reviewed the literature on the treatment of brucellosis prior to 1936. They concluded that the bacteriostatic effect of dyes on *Brucella abortus* and *melitensis* has been demonstrated in vitro but that their clinical use is unjustified. It was impossible to inject sufficient amounts intravenously to obtain a concentration that would injure the infectious agent in vivo They pointed to their observation[119] that *Brucella abortus* could be isolated from guinea pigs injected with lethal doses of acriflavine and methyl violet Simpson[630, 634] considered them and other similar chemicals of doubtful value. More effective measures are now available in any event

Para-aminobenzoic acid has been used in acute and in persistent chronic *Brucella* infection with inconclusive results Its use apparently was suggested by the demonstration of the intracellular growth of *Brucella* (p 98) and by the observations of Cotton and her associates[144] on experimental infection in guinea pigs.

Atabrine was reported to have in vitro activity against *Brucella*,[101] with temporary benefit in clinical use. Its effect may confuse the differential diagnosis of malaria from chronic brucellosis.

Colloidal manganese and *hydrochloric acid* for intravenous use are mentioned as examples of apparently worthless preparations which have been exploited as almost specific means of cure. Reports of their use have been unconvincing, both as to accuracy of the diagnosis in the patients treated and as to results claimed

Neoarsphenamine given intravenously was reported[691] as having been followed by prompt subsidence of the acute illness in 6 of the 7 patients treated, following the second dose. No reports on its use in the chronic illness have been encountered. It was employed in 7 patients in the chronic phase of the illness by the author without noticeable effect. In 2 patients, chronic brucellosis and syphilis coexisted, necessitating the use of long courses of neoarsphenamine. Addition of *Brucella* vaccine to the treatment regimen was followed by clinical response. In the light of present evidence it would seem useless in the chronic illness These views were confirmed by Wainwright[692] who stated that no follow-up reports on his patients were possible. However, his results in 2 or 3 additional acute infections treated since 1937 gave similarly satisfactory early response He confirmed the lack of value of the drug in the chronic illness.

Sulfonamide Compounds

Sulfonamide compounds have been the subject of numerous conflicting reports Sulfanilamide, neoprontosil, sulfapyridine, sulfathiazole, sulfamerazine, and sulfadiazine all are likely to aid in terminating the acute illness, although relapse of the acute illness or supervention of a chronic phase may not be prevented None of the compounds can be depended upon for uniform effects in all cases, but their value should not be minimized In the chronic illness, the effects of the sulfonamides are extremely variable, with apparent curative effects occurring in but a small per-

centage. Sulfaguanidine, sulfasuxidine, and sulfathalidine may be of value in intestinal *Brucella* infection

In 8 cases treated with sulfonamides by Spink and Hall,[643] all of whom had a bacteriemia due to *Brucella abortus,* 5 recovered completely and all except 1 remained well for one or more years following treatment. This patient recovered after a second course Of the 3 patients who failed to respond, 1 had a *Brucella* endocarditis and the other 2 had toxic reactions necessitating withdrawal of the drug *The bacteriemia was eradicated in every instance coincident with the use of the sulfonamide except in the patient with* Brucella *endocarditis.* Five of the 8 patients had the chronic form of the disease and 3 the acute form All patients were febrile They considered that the sulfonamides were of little or no value in chronic cases without bacteriemia and were doubtful of its value in *Brucella suis* bacteriemia, in agreement with Wise [715]

Eighteen patients without demonstrable bacteriemia but with other evidence of infection were treated by Spink and Hall Five were acutely ill and all recovered and remained well for more than a year Thirteen were in the chronic phase, 9 of these had complete remission of symptoms for one or more years. Four failed to respond to sulfonamide therapy, 2 of these responded to artificial-fever therapy

Simpson [633] pointed out that the value of sulfonamide compounds must be regarded as undetermined and that a temporary remission is not synonymous with cure.

Dosage of the sulfonamide compound employed and its use over a sufficient length of time may be the deciding factors in its effectiveness In the acute illness a successful regimen has consisted of administration of full dosage (sufficient to maintain an adequate blood level) until febrile reaction and the major manifestations were well under control, then gradual reduction over a period of several weeks. Alkalinization of urine is, of course, necessary along with large fluid intake *Unless there has been an adequate spontaneous phagocytic response vaccine therapy is begun before the drug is withdrawn and is continued until there*

has been good phagocytic response to vaccine. This regimen is calculated to prevent relapse of the acute illness and also to control the chronic phase which so often follows. When treatment is initiated in the chronic phase a similar regimen is instituted.

INDIVIDUAL SULFONAMIDE COMPOUNDS

Sulfanilamide (*p*-amino-benzene-sulfonamide) was reported on favorably by many.[53, 63, 64, 243, 286, 341, 461, 511, 613, 650, 666, 674, 701] Most of the patients were in the acute phase of the illness. Failure in the presence of *Brucella endocarditis* has been uniform [167, 638, 642]

Sulfanilamide in chronic brucellosis was strikingly successful in one of the author's patients in whom *Brucella* vaccine therapy was ineffective. He has remained symptom-free for eight years Its effectiveness in the majority of other patients was not notable.

Horn [341] reported on the treatment of 54 patients with sulfanilamide and its derivatives, only 2 of which were acute cases. He believed that smaller than usual dosage over a longer period of time has a more favorable effect—20 gr. daily for twenty-five days, repeating the course every other month (or on alternate weeks). The average total was 500 gr The amount was the largest possible without too great toxic disturbance. He also used vaccine in these patients, concomitantly and following the course of sulfanilamide, believing that the two methods complemented each other

Relapse followed use of sulfanilamide in each of 6 cases reported by Bynum [102] Two were acute infections, 1 was subacute, and 3 were chronic His uniformly poor results may have been attributable to the small dosage employed The tendency to relapse was also noted by Long and Bliss,[444] who surmised that their results might be attributable to freshness of infection in their patients It would seem that recent infections should yield most readily

Persistence of positive blood cultures for two months, in spite of prompt clinical recovery following use of sulfanilamide for his own acute illness, was reported by Van Wagenen [663]

Increased phagocytosis was attributed by Welch, Wentworth, and Mickle[104] to the action of sulfanilamide. They expressed the belief that sulfanilamide acted directly in *Brucella* infections by increasing the opsonic power of the blood In the author's cases no phagocytic response to sulfanilamide was noted beyond that which might naturally occur in response to infection.

Neoprontosil (azosulfamide) may be as effective as the other sulfonamide compounds and, in some patients sensitive to sulfanilamide, may be well tolerated.[39, 332] It was especially valuable in 2 of the author's patients with severe, acute, multiple joint involvement. One had been extremely sensitive to *Brucella* vaccine even in high dilutions Apparent response to neoprontosil began within forty-eight hours and all involved joints had completely subsided within a week. The drug was continued for three weeks. There has been no recurrence in the ensuing seven years The second patient was a veterinarian who had proved refractory to *Brucella* vaccine, multiple joint swelling and lameness, as well as myalgia and fatigue, yielded promptly following administration of 40 gr. daily He was not followed for more than one year.

Sulfapyridine (2-sulfanilamido-pyridine) was apparently the means of terminating a severe acute exacerbation in a 70-year-old woman in whom sulfanilamide and neoprontosil had produced toxic effects Prompt remission occurred in one other aged female patient following replacement of sulfathiazole by sulfapyridine. This sulfonamide failed to induce remission in a recurrent chronic infection in another patient who responded favorably to *Brucella* vaccine

Sulfathiazole (2-sulfonamidothiazole) was used successfully in 3 patients, acutely ill with the *suis* strain, who had reacted unfavorably to Brucellin.[74] It has proved to be about as effective as other sulfonamides

Sulfaguanidine (p-aminobenzenesulfonylguanidine monohydrate) was administered in 3 patients suffering from febrile attacks of brucellosis by Sarvis,[601] with prompt remission in all Dosage was 9 Gm daily for 3 to 6 days, then 3 Gm daily Periods of observation were from two and one-half months to ten months.

He considered that the bowel was not the only focus of infection but that the drug must be effective even though absorbed in only extremely small amounts.

Sulfasuxidine (succinylsulfathiazole) was reported as having excellent effects in 16 of 18 cases,[163] using only 0 5 Gm. 3 times daily, apparent cure in 10 and marked improvement in 6, with no response in only 2 patients, was reported. Even in full dosage (10–15 Gm. daily) this drug failed to influence favorably any of the 14 patients for whom it was prescribed by the author. In one of these patients intestinal localization was proved by stool culture. The use of this sulfonamide, which is absorbed from the intestinal tract in only negligible quantities, is suggested in known or suspected intestinal localization of infection, along with other measures to increase the patient's immunologic response.

Sulfamerazine (2-sulfanilamido-4-methylpyrimidine) may have some advantages over the other sulfonamide compounds because of relatively low toxicity, rapid attainment of high blood concentration, slow excretion, and smaller dosage. It is known to pass readily into cerebrospinal, abdominal, and pleural fluids, suggesting its possible value in localized *Brucella* infections of the meninges, pleura, or peritoneum, as with sulfadiazine and other sulfonamides Initial dosage for the adult usually is 3 0 to 4 0 Gm, then 1 0 Gm every eight hours, in children over 3 years, the usual initial dose is 1 5 Gm, then 1 0 Gm every twelve hours. Alkalinization of urine is necessary It failed to bring about improvement in 2 of the author's patients in the presence of bilateral salpingitis complicating chronic brucellosis.

Sulfadiazine (2-sulfanilamidopyrimidine) apparently was successful in controlling each of three severe acute episodes in a 64-year-old woman but did not prevent relapse When vaccine therapy was instituted following the third relapse the patient remained well over a period of three years There was prompt recovery following administration of sulfadiazine in 1 patient with recurrent meningo-encephalitis (diagnosis not proved by culture) This patient was intolerant of sulfathiazole. Sulfadiazine failed to influence the course of the recurrent acute illness in 1 patient

with extreme hyperpyrexia (p 157). Use of streptomycin was followed by prompt remission

Eleven of 17 acutely ill patients who had contracted their infections through contact with *Brucella suis* or *melitensis* (about equally divided) were treated with sulfadiazine for periods of twenty to thirty days, in dosage sufficient to maintain blood levels well in excess of concentrations required to inhibit the growth of *Brucella suis* in vitro [345] There was no clear-cut, abrupt amelioration of symptoms in any. Although temperatures returned to normal in one to eleven days after initiating treatment, with no marked elevation subsequently, all 11 patients suffered one or more relapses after cessation of treatment. Blood cultures during these relapses were positive in 7, negative in 3, and not studied in 1. No demonstrable decrease in sensitivity to sulfadiazine in vitro was noted as a result of therapy.

Failure of sulfadiazine to bring about lasting remission was reported by Pulaski and Amspacher [350] in 17 patients, 7 in the acute and 10 in the chronic phase Blood cultures were positive for *Brucella* in 6 of the 7 acute illnesses and in 1 of the 10 chronic cases. These patients later were treated with streptomycin alone and in combination with sulfadiazine Two recovered under the combined therapy (p 440).

Combined use of various sulfonamides to lessen the tendency to renal damage through crystalluria and nephrotoxic action has been suggested [227, 430, 431]

In summary it may be said that the greatest value of the sulfonamides lies in helping to terminate the acute illness, alone or in combination with other specific methods of treatment, particularly transfusions of immune blood and streptomycin Failure of sustained phagocytic response concomitant with recovery points to the wisdom of bolstering the patient's specific resistance to *Brucella* infection This procedure is stressed because of the likelihood that the organism has not been eradicated and that relapse will occur.

ANTIBIOTICS

Penicillin has not fulfilled the hope that *Brucella* might be the exceptional Gram-negative organism that would yield to it. Tsun T'Ung[678] found that penicillin "exerted a considerable antibacterial action on 8 out of 15 strains of *Biucella* in vitro" and that "this action was enhanced by the combination of penicillin with a small amount of sodium sulfathiazole." He felt that it was possible that some of the antibacterial action of the penicillin preparation used was due to the incidental presence of penatin. In view of Kochalaty's[404-407] failure to reproduce his own earlier observations as to the apparent efficacy of penatin against *Brucella*, it is unlikely that its incidental presence could have accounted for T'Ung's results[656] All other opinions and reports have been uniformly unfavorable.[225, 330, 331]

Shwartzman[629] mentioned experiments which demonstrate that the penicillin susceptibility of highly refractory Gram-negative organisms (*Eberthella*, *Salmonella*, *Shigella*, and *Brucella*) is greatly enhanced by the addition of the amino-acid methionine 309 and methionine sulfoxide.

Penicillin and sulfadiazine combined were given to 2 patients acutely ill with *Brucella suis* infections contracted in the course of laboratory work;[illegible] penicillin was given intramuscularly and sulfadiazine orally for twelve and nine days respectively One had a short relapse with positive blood culture subsequent to treatment and then remained well for a period of observation of about two years The second patient apparently recovered completely but was not observed for as long a period Dosage used was 3,500,000 units of penicillin and 64 Gm sulfadiazine in a period of twelve days The second patient received 2,100,000 units of penicillin and 54 Gm sulfadiazine in a period of ten days. It is probable that any effect obtained was attributable to sulfadiazine.

Streptomycin is excreted into the bowel in only very small amounts when given parenterally, and is only slightly absorbed from the bowel, giving insignificant blood levels, when admin-

istered orally. It is largely excreted in the urine. Following parenteral injection it was found to be distributed throughout most body fluids, including blood, urine, ascitic fluid, pleural fluid, aqueous and vitreous humor, amniotic fluid, and bile, with small amounts present in the spinal fluid.[17, 740] No evidence of hepatic or renal damage from single massive doses was found. The failure of the drug to date to bring about more than temporary bloodstream sterilization in brucellosis in spite of its wide distribution and its known specificity against *Brucella* may be due to the localization of *Brucella* within granulomatous lesions and its intracellular growth.[236]

A definite bacteriostatic effect of streptomycin against *Brucella abortus* was reported by Live, Sperling, and Stubbs,[441] following two studies in experimentally infected guinea pigs.

There have been several reports [236, 331, 335, 339] of failure of cure of any case of brucellosis, but definite clinical improvement while streptomycin was in use and for varying periods of time thereafter. All cases treated were in the acute phase. Herrell quoted Heilman as being able to save the lives of animals inoculated with *Brucella* but inability to eradicate the disease. The organisms remained in the spleen.

In a later report made by Herrell and Nichols,[333] a complete and apparently lasting recovery occurred in 1 of their patients, but only after removal of the probable focus of infection:

> A veterinarian had been ill for a year before admission to the Mayo Clinic. For the first six months his symptoms had been of a chronic

> admitted to the Mayo Clinic with almost continuous high fever, sweats, chills, and a steady downhill course. He had lost 40 pounds in weight Blood-agglutination reaction by then was positive in a 1 160 dilution. He was given streptomycin by intravenous drip, 1,000,000 units daily for twenty days Temperature continued from 101 to 102° F. but became normal for a few days, beginning on the ninth day of treatment. He gained 17 pounds after this course of treatment and

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A veterinarian had been ill for a year before admission to the Mayo Clinic For the first six months his symptoms had been of a chronic nature, with low or negative agglutinin titers He became acutely ill in December, 1944, and entered the Albany Hospital in January, 1945, where a diagnosis was established by blood culture Later he was admitted to the Mayo Clinic with almost continuous high fever, sweats, chills, and a steady downhill course. He had lost 40 pounds in weight. Blood agglutination reaction by then was positive in a 1:160 dilution. He was given streptomycin by intravenous drip, 1,000,000 units daily for twenty days Temperature continued from 101 to 102° F. but became normal for a few days, beginning on the ninth day of treatment He gained 17 pounds after this course of treatment and

the spleen was reduced in size. Blood culture became negative. Symptoms then recurred and blood culture again became positive. A second course of streptomycin with 2,000,000 units daily was then begun by intravenous drip for seven days, by which time blood culture again was negative. Symptoms again recurred and the spleen remained enlarged. It was considered to be a focus of infection and was removed. *Brucella* was recovered from splenic emulsion postoperatively. Postoperative blood culture was still positive. He was then given 1,000,000 units of streptomycin daily for nine days, after which blood culture became negative and remained so. He made an uneventful recovery and reported four months later that he was well, afebrile, and had regained the 40 pounds of weight loss. (In a personal communication nearly two years later, this patient informed the author that he was "enjoying excellent health.")

In this result it is probable that splenectomy played an essential role, in view of the tendency to relapse following each of two previous courses of streptomycin and the demonstration that the spleen was the site of localized infection. It is possible that larger initial doses of streptomycin would have had more lasting, if not curative, effect, especially if combined with a sulfonamide.

Splenectomy was performed under somewhat similar circumstances in a patient who had relapsed following temporary response to each of several courses of streptomycin; mild relapse occurred at the end of eighteen months. In this instance blood culture had been negative but splenic involvement had been demonstrated by enlargement and tenderness and by direct visual examination through the peritoneoscope. The omentum was found to be wrapped around and adherent to the spleen. The spleen showed no characteristic changes of *Brucella* infection. Culture was negative. (See pages 157 and 286.)

Phagocytic response was marked within five days following the favorable response to streptomycin in one acutely ill patient. Its mechanism is not clear. A similar phagocytic response following use of streptomycin occurred in a patient reported by Lowbeer [447]

Two other patients treated by Herrell and Nichols had doubtful results. In 1 there was a possible complicating endocarditis, blood

cultures became negative but further observation was considered necessary. In the other patient blood culture also became negative but symptoms persisted.

Experiments on the excretion of streptomycin in the bile[734] suggested the possible efficacy of streptomycin in *Brucella* infection of the biliary tract, in the absence of obstructive jaundice. [illegible]

[illegible] of acute cholecystitis and empyema, nearly always associated with obstruction of the cystic duct, it was considered unlikely that streptomycin would be of value The usefulness of the agent in any given case of chronic cholecystitis with stones was considered uncertain since any such organ may become obstructed at any time The antibiotic agent was excreted in high concentration in the hepatic bile of patients who had normal livers.

Three of the 17 acutely ill patients with laboratory infections (due to *Brucella suis* in 2 and *melitensis* in 1)[345] were treated with streptomycin hydrochloride, intramuscularly or intravenously. Dosage used was 810,000 units within a period of three days and a second course of 15,800,000 units within a period of eight days during an exacerbation about one month later, in one patient. This patient had a prolonged relapse lasting five months following the second course of streptomycin and was still severely ill at the end of two years of follow-up during which time cultures were positive. In a second patient 23,000,000 units were given within six days, also without apparent response, although this patient later was reported back at normal activity, with no fever but with "mild occasional symptoms" at the end of about eighteen months. The third patient (suffering from a *melitensis* infection) received one course of 20,500,000 units within six days during the second acute episode and had a third acute exacerbation about two weeks after streptomycin was stopped Sulfadiazine was given for this relapse over a period of one month Blood culture did not again become positive and there was no return of symptoms at the end of about eighteen months of observation.

Howe and Heyl[544] stated that streptomycin had only been of benefit in patients in whom blood levels had reached or exceeded 20 to 30 μg. per cc. or in whom the daily dose at any time approached 6 Gm. They reported one acute infection treated with 6 Gm. daily for ten days, with freedom from symptoms lasting through fifteen months of observation. There was, however, minimal residual disturbance of eighth nerve function.

An intensive effort to treat acute and chronic brucellosis with streptomycin was made by Pulaski and Amspacher.[550, 551] Seven of these cases were in the acute phase and 10 cases in the chronic phase. (Patients exhibiting fever and symptoms for a year or more were designated as chronic) Blood cultures were positive for *Brucella* in 6 of the 7 acute cases and in 1 of the 10 chronic cases. Patients were treated with streptomycin for periods varying from ten to forty-seven days in the acute phase and from three to ten days in the chronic phase Total dosage varied from a minimum of 10 Gm. to a maximum of 141 Gm. in the acute illnesses, and from 2 Gm. to 37.3 Gm. in the chronic illness. The organisms were found to be highly susceptible to streptomycin in vitro (0.5 to 1.0 μg./cc) There was failure to bring about cure in any.

STREPTOMYCIN AND SULFONAMIDE COMPOUNDS COMBINED

In 2 patients in whom streptomycin alone and sulfadiazine alone had failed to bring about recovery, complete remission in both followed administration of streptomycin and sulfadiazine given concomitantly. Dosage of streptomycin was 3 Gm daily and of sulfadiazine 6 Gm daily, for twenty-one days. They had remained well for periods of six and eight months respectively at the time of the report

It was pointed out that *Brucella* infections are characterized by the distribution of organisms through the lymphatics and the blood stream, with possible localization in the gallbladder, spleen, and lymph nodes, in addition to other foci. In cases in which death occurred in the course of treatment streptomycin was not found in lymph nodes in assayable amounts, while only small

amounts could be recovered from the parenchyma of the spleen. Sulfadiazine is known to penetrate all body fluids.

The rationale of combined use of a sulfonamide and streptomycin may lie in part in the development of drug resistance on the part of the organism to one of the two therapeutic agents but the continued effectiveness of the other. Clough[143] stated that the few variants of *H. influenzae* which are resistant to streptomycin retain their sensitiveness to sulfonamides, affording a better chance of eliminating the infection if both drugs are used. Apparently, also, smaller and less toxic dosage of streptomycin may be employed under such combined therapy.

Later Pulaski[515] reported prompt remissions in 3 of 4 additional patients who received combined streptomycin and sulfadiazine therapy for an average of seventeen days. In the fourth patient it was difficult to state whether the remission was due to the drug, or whether it was a part of the natural course of the disease.

The first apparent cure of a chronic infection with combined use of streptomycin and sulfadiazine was reported by Harris and Jett:[312]

A 42-year-old farmer complained of fatigue, sweating, epigastric discomfort, and severe headache in September, 1946 Symptoms had recurred at irregular intervals for several weeks but headache had been quite constant, coming on at about 9 or 10 A.M. and persisting until about 4 P.M. daily. Fever ranged from 99 to 100.8° F. (oral). Other likely causes for his illness having been excluded, brucellosis was strongly suspected. Blood-agglutination reaction with *Brucella* occurred in a 1:1280 dilution on September 28, 1946. Other laboratory study was negative or noninformative, as was physical examination.

He was referred to the author on October 7, 1946, for confirmation of diagnosis and for advice as to treatment. His only verbalized complaints were that he was "a little damp," and that he had "neuralgic headaches and stomach upsets." It required questioning to bring out that fatigue had been marked, that he had had a stiff elbow for a month or two in February, 1946, with no swelling, redness, or local heat, that he had been stiff all summer after heavy lifting, and that libido had lessened.

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teen days.* A total of 44 Gm. of streptomycin was used. The dosage of sulfadiazine was sufficient to maintain a blood level of 5 9 to 6 3 Gm

At the end of forty-eight hours of this regimen the patient was entirely free of fever and all symptoms referable to brucellosis and has remained so through the subsequent two years of observation Blood culture was negative when repeated in November, 1947.

Other chronic cases are under observation after treatment by the two drugs, with favorable early response.

Pulaski [549] later furnished additional data, including follow-up reports on patients treated with the combined drugs. Seven patients had completed a course of treatment with 3 Gm. of streptomycin daily, together with 6 Gm. of sulfadiazine daily, for an average of twenty-one days. Two patients were symptom-free eighteen months following treatment. A third patient remained well for nine months except for arthralgia apparently unrelated to brucellosis. In 2 other patients relapses occurred on the seventh and twelfth week after treatment, a second course was not given because both patients had suffered moderately severe vestibular symptoms. A sixth patient remained well during the three months of observation A seventh patient, in whom blood culture was never positive, was uninfluenced by the combined therapy.

Eisele and McCullough [159] and Spink and his coworkers [611] also reported successful treatment of the acute illness by these methods, using shorter periods of treatment. In view of the relapses noted by Pulaski in 2 patients after more prolonged treatment, the advisability of shorter courses may be questioned

In two early reports by Keefer and his associates [307, 309] compiled from fifty-five investigations, treatment of 45 acute infections with streptomycin alone was reviewed, 30 showed a decrease in fever while under treatment and 15 showed no effect in the course of the disease while receiving streptomycin Of the 30 showing decrease in fever, 29 were followed for from three to eight weeks, 2 relapsed The average dose in 25 cases was 3 or 4 Gm daily for from five to sixteen days Five patients received

* The advisability of decreasing dosage remains in doubt The importance of adequate initial dosage has been established

He had been born and had always lived on a farm in southern Maryland His cattle had never aborted and tests had always been negative for brucellosis. However abortion had occurred among his swine, one sow had lost two successive litters in March and June of 1946, each time about halfway through the gestation period.

Physical examination was essentially negative. Laboratory studies showed no anemia, a white blood count of 5,500 with 46 per cent polymorphonuclear neutrophiles, 2 per cent eosinophiles, 51 per cent lymphocytes, and 1 per cent basophiles. Sedimentation rate was 45 mm /1 hour (Westergren). Microscopic and macroscopic blood-agglutination reactions with *Brucella* were positive, the latter in a 1:640 dilution. Opsonocytophagic reaction showed marked phagocytosis in 0 cells, moderate in 0 cells, slight in 17 cells, and none in 8 cells, a numerical index of 17. No skin test having been performed previously, it was then done using 0 1 cc. of Brucellergen in 1:12,000 intradermally in one arm and 0 1 cc of heat-killed *Brucella abortus* organisms in the other arm *The Brucellergen reaction was negative at the end of twenty-four and forty-eight hours and subsequently. Reaction to heat-killed* Brucella abortus *organisms was positive*

Blood culture yielded *Brucella suis* Streptomycin susceptibility studies showed the organism to be susceptible to 1 unit of streptomycin, i e, it was five times as resistant as standard.

Brucella abortus vaccine was advised as a preliminary method, to be followed by streptomycin and sulfadiazine if necessary Vaccine was administered in a dilution of 1·100 intramuscularly, beginning with 0 1 cc on October 22, 1946, and ending on November 8, 1946 Following this regimen the patient resumed his farm work, improved but not fully recovered and still with fever ranging from 99 8 to 100 8° F. each afternoon On one occasion in November, 1946, Dr. Jett reported that the spleen was palpable.

In June, 1947, about one year after the onset of symptoms referable to brucellosis, because of continued low-grade fever, fatigue, and muscle and joint pains, the plan for use of streptomycin parenterally and sulfadiazine orally was put into effect Treatment was begun with 4 Gm of streptomycin and 6 Gm of sulfadiazine daily After five days of this dosage of streptomycin it was reduced to 2 Gm daily for three days and then to 1 Gm daily for the remainder of the period of nine-

development of resistance in vivo, and localization of infection in an area that cannot be reached.

Development of resistance apparently may occur in either of two ways.[149] Exposure to a sublethal concentration of the drug might bring about an adaptation as the result of a gradual progressive change in the metabolic activities of the organisms. Another mode of action may operate in killing or inhibiting the growth of the sensitive organisms, while permitting a few initially resistant organisms to survive and multiply. The latter hypothesis is the more likely because of the great rapidity with which a strain may become resistant. The obvious implication that drug-resistance is more likely to develop when inadequate dosage is employed has been borne out by clinical observation.

Toxic effects noted included skin eruptions, fever, eosinophilia, and neurologic disturbances (particularly vertigo). They were attributed to histamine-like reactions due to impurities but were also noted when the pure crystalline preparation was used In one of the author's patients low-grade fever decreased under combined streptomycin and sulfadiazine therapy but did not return to normal levels until thirty-six hours after streptomycin was stopped. Since sulfadiazine was continued it is probable that the fever was due to streptomycin

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less than 3 Gm. daily. Of the 15 patients who showed no improvement, 10 received only 2 Gm. daily and the remaining 5 received 3 to 4 Gm. daily. No dramatic effects were observed in the course of the disease but the patients were followed for an insufficient period to determine the effect of streptomycin on the relapse rate No studies were made on cases of chronic brucellosis because of the limitation of supplies of streptomycin.

Minimum dosage recommended was 4 Gm. per day for fourteen to twenty-one days. It was suggested that a group of patients be treated for from fourteen to twenty-eight days with the maximum tolerated doses to determine whether or not the relapse rate could be reduced and the total duration of the illness shortened. They considered the optimum dose to be that amount which will bring the infection under control and assist in the sterilization of the focus of infection. All 3 strains of *Brucella* were found to require a concentration of 0 5 μg./cc. to inhibit growth. However, many strains of organisms susceptible to 5 or 10 μg./cc. acquired resistance in vivo to from 200 to as much as 50,000 μg./cc The maintenance of a concentration of streptomycin in the blood of four to eight times that necessary to inhibit the organism in vitro completely was advised The usual maximum dose tolerated by most patients was 4 to 6 Gm. daily although as much as 10 Gm. daily was given to a few patients without ill effect.

McDermott was quoted as having used crystalline streptomycin sulfate, 3 Gm daily for a period of three months, noting local irritation at the site of injection and. in 9 of 10 patients, many hyaline and granular casts but with no other evidence of renal impairment.

Routes of administration recommended were intramuscular, subcutaneous, and topical, including intrathecal, intraperitoneal, and intrapleural They considered the intramuscular route the one of choice for systemic treatment. Oral administration was useless although there was great reduction of the numbers of streptomycin-susceptible bacteria in the bowel.

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lowed. In a third patient toxic effects appeared on the fourteenth day but were erroneously attributed to the sulfonamide and streptomycin was continued for another week. Marked vertigo and instability of gait persisted for two weeks and then slowly subsided in the course of another three weeks. There is increasing evidence that the toxic effects of streptomycin are often ignored *It is essential that the drug be discontinued at the first sign of intoxication, to avoid possible permanent changes in eighth nerve function.*

Brown and Hinshaw[83] cautioned: "When large doses of streptomycin are being used the physician must be on the alert for a low-pitched continuous tinnitus which indicates the onset of nerve deafness for low tones Discontinuance of administration of the drug at the onset of tinnitus probably will prevent the development of serious deafness" Audiograms before and during treatment seem advisable

No reports have been made on the administration of streptomycin in any vehicle intended for repository effect.

At present it seems in accordance with good judgment and safety to offer the use of combined therapy with streptomycin and sulfadiazine in early infections, in the hope that the organism can be completely eradicated before it has become entrenched, or in late infections in which more conservative and less rigorous measures have failed. Dosage must be guided by response and by possible toxic effects

OTHER ANTIBIOTICS

Beal[44, 45] found that filtrates of thirteen mold cultures possessed activity against *Brucella* in vitro The active material from one of them, tentatively identified as *aspergillus terreus,* after partial purification, inhibited growth of *Brucella abortus* in a dilution of 1:64,800 Studies to determine toxicity were under way.

Further advances are to be expected but reports must be accepted with caution Although polymyxin gave great early promise there is growing evidence of its nephrotoxicity. Larson and

Carle * were unable to show any curative effect from it in guinea pigs experimentally inoculated with *Brucella suis*. Aureomycin is under clinical investigation by the author, it is administered orally or parenterally. Early observations in animals and man have shown it to be non-toxic and apparently as effective as streptomycin against *Brucella* (See Addenda, p 531.)

Special Treatment of Certain Localized Infections

Central-nervous-system involvement may be favorably influenced by the sulfonamide compounds (p. 236), by human immune serum,[540] by streptomycin, or by their combined use. Because of possible focal reactions, perhaps irreversible, the use of vaccines or toxic filtrates seems of doubtful wisdom, except under exceptional circumstances and then with great caution In one of the author's cases there was exacerbation of neurologic signs following attempts to immunize against further attacks after recovery, even with the use of very dilute *Brucella abortus* bacterin. In another patient, an elderly woman with no evidence of intracerebral pathology, except for headache of a nonlocalizing character, *Brucella abortus* vaccine was given in reactionless dosage A mild apoplexy or arterial spasm occurred about two hours following the third dose, with blurred vision, numbness and tingling of hands, mental confusion and dysarthria, lasting for forty-eight hours, perhaps by coincidence or perhaps on the basis of allergic reaction Treatment with bacterial antigen complex was followed by recovery, with no untoward focal reactions.

Brucella endocarditis deserves an intensive trial with full doses of streptomycin and sulfadiazine concomitantly, or with other antibiotic such as aureomycin or chloromycetin, because of the failure of other methods to influence it favorably

Salpingitis and other localized manifestations of *Brucella* infection are discussed on page 424, under physical therapeutic

* Larson, C L, Carle, B N, and Verder, A E The effect of polymyxin in the treatment of experimental brucellosis and tularemia *Ann New York Acad Sc* 51 982, 1949

measures. Surgical procedures do not seem warranted unless conservative measures (short-wave pelvic diathermy, vaccine therapy, antibiotic and chemotherapy) fail.

Biliary tract infections may be amenable to streptomycin under some circumstances (p. 439).

Extirpation of the gallbladder is a justifiable procedure if *Brucella* infection is demonstrated by culture of aspirated bile or if there is radiographic and clinical evidence of disease of the viscus. No prognosis may be made as to cure since there may also be localized infection elsewhere.

Intestinal localization of infection has been treated by thionine and methyl violet,[427] orally and by enemas, with reported success. A sulfonamide orally and streptomycin orally and parenterally seem indicated in such circumstances, in the light of present knowledge. Aureomycin or chloromycetin may prove effective

Splenic infection often presents one of the most involved problems. If there is clinical or cultural evidence of splenic localization in a patient who is refractory to treatment with sulfonamides, streptomycin, vaccine, and perhaps also to roentgen rays and artificial fever therapy (separately or in combination) splenectomy may be indicated. Each case must be carefully evaluated.

Spink[641] stated that splenectomy is rarely indicated. He quoted one patient in whom splenectomy was performed, although a previously positive blood culture became negative, there was no change in the clinical course of the disease. There were typical granulomatous changes in the spleen but the organism could not be isolated from splenic pulp This experience suggests that other localization of infection (e g retroperitoneal lymph nodes) or persistent allergy may have prevented recovery.

Pernokis[531] stated that the functions of the spleen are very vague and that removal is compatible with a long and healthy life. Hematopoiesis and regulation of the blood flow to the gastrointestinal tract during digestion, through its rhythmic constriction, seem to be accepted functions but its role in the destruction of red cells he considered doubtful It should be considered a serious operation, even in the hands of expert surgeons, requiring

careful preoperative and postoperative care. He considered a careful search for accessory spleens to be important. Hyperplasia of the lymphoid and reticulo-endothelial tissue elsewhere in the body compensates for splenic loss, with hyperplasia of the lymph nodes a not uncommon aftermath

Rosenthal [556] hesitated to recommend splenectomy since the organ may have some function which helps in combating infection. He cited 2 cases of splenectomy for malaria in whom severe attacks of malaria followed; in 1 an accessory spleen, enlarged almost to the size of the original organ, was found. He suggested experimental splenectomy in infected animals as a means of further investigation.

Involvement of individual vertebrae and/or intervertebral discs, causing back pain with or without sciatic neuritis may be relieved by spontaneous healing during bed-rest or the process may be hastened by artificial fever therapy or roentgen ray therapy. Rapid recoveries have occurred following specific vaccine therapy, even in the presence of the typical herniated intervertebral disc syndrome (p 231). It must be assumed that the process is one of nerve-root irritation caused by infection rather than by mechanical pressure alone under these circumstances Prolonged bed-rest may fail to bring about recovery if *Brucella* infection remains active Surgery does not seem indicated unless mechanical pressure is demonstrated and conservative treatment measures have failed.

Transfusion of Immune Blood

Creswell and Wallace [150] reported recovery of 2 acutely ill patients after transfusion of unaltered blood from donors whose blood showed high opsonic indices The patients had shown low opsonic indices before transfusion and high indices afterward Quevli and Nelsen [553] had used donors who were thought never to have had the disease, attributing the results to natural immunity (It is more probable that these patients had had previous infections, subclinical in nature, which brought about phagocytic

response) Whole blood was used to avoid possible interference with the immune properties of the donor's blood.

This method was employed in one of the author's acutely ill patients in whom streptomycin had induced remission but who had relapsed with a very severe illness when further supplies were not obtainable (p. 157). The donor chosen was one who had been free of any evidences of *Brucella* infection for more than two years after recovery from a prolonged chronic illness; she had maintained a high phagocytic activity against *Brucella* Citrated blood was used for technical reasons. The patient's blood, which had previously shown low phagocytosis of *Brucella*, revealed a moderate rise in phagocytosis following the transfusion. Remission began in about twenty-four hours and a course of *Brucella vaccine was then administered.*

The same donor's blood was used for an elderly female patient whose subacute febrile illness had persisted for three months in spite of treatment with sulfonamide compounds and an attempt at active immunization. No improvement followed. Recovery followed use of a *Brucella* bacterial antigen complex (B A.C).

Transfusions of blood serum from the pooled blood of 10 patients, all of whom had recovered from *Brucella suis* infection, failed to influence the course of a case of infection with *Brucella suis*, causing endocarditis, nephritis, and death from rupture of a mycotic aneurysm.[167]

History of recovery from brucellosis is insufficient proof of the donor's immune status. Opsonins commonly disappear from the blood following recovery Determination of the phagocytic power of the prospective donor's white blood cells should result in the most effective selection

The possible danger of the recently recovered donor having *Brucella* organisms in the blood stream must be considered Introduction of a more virulent strain, such as *melitensis* or *suis*, in a recipient who is having difficulty in combating a less virulent *abortus* infection could be disastrous.

Since transfusions of immune blood may confer only temporary passive immunity, its use should be accompanied or followed by

attempts at active immunization or by use of methods aimed at eradication of the organism

Transfusions of nonimmune blood appears to have no rational basis beyond its nonspecific effect, whether or not combined with administration of a sulfonamide compound Favorable effects noted may be due to the sulfonamide alone, or the "nonimmune" donor may in fact be immune by virtue of unrecognized past infection.

Intramuscular Injection of Convalescent Whole Blood

Kennan[393] reported remission of an acute illness in 1 patient following a single intramuscular injection of 15 0 cc of convalescent whole blood. Carpenter and Boak[120] reported treatment of 1 patient with intramuscular injection of 50 cc. of human convalescent serum and 1 with 200 cc of whole human blood, obtained from a donor who had recovered from brucellosis and whose blood agglutinins were still present in a titer of 1:320 Both recovered in about two weeks. The simplicity of the method suggests its further trial.

Autoserum Therapy

There is little evidence of the value of this procedure Good results in 2 of 5 cases were reported by d'Oelsnitz and Liotard[179] From 2 to 5 cc. of serum from the patient's blood were injected subcutaneously at the onset of a febrile period Successful use of this method in 2 patients was reported by Beattie and Rice[46]

Intrathecal Use of Human Immune Serum

Human immune serum given intrathecally was followed by recovery in the 2 patients reported by Poston and Smith.[540] One patient was a 50-year-old woman, the other a 7-year-old girl, both with central-nervous-system involvement. The serum used in both cases was obtained from one of the authors who had had prophy-

lactic doses of killed *Brucella* organisms eight years before (this donor may have been more thoroughly immunized by infection contracted in the course of laboratory work than by the inoculations). The adult patient was given three intrathecal injections totaling 74 cc. within four days.

The donor's serum agglutinated the organisms isolated from the patient's spinal fluid. The immune status of the donor's serum may be further evaluated by the opsonocytophagic reaction.

Antiserum

The early use of *anti-melitensis* goat and horse serum was described by Aldridge.[6] Results were variable. Favorable results were reported by others.[416, 671] O'Neil[520] and Wherry, O'Neil, and Foshay[708] reported therapeutic trials of an antiserum produced by inoculation of goats, first with mixed bovine and porcine strains, later also using caprine strains, detoxified by nitrous acid or produced by use of a formaldehyde-killed antigen. Twenty acutely ill patients made satisfactory recoveries and were known to remain well for periods varying from four months to twenty-nine months. Results in 2 others were questionable and in 4 no improvement was noted. Of those who made good response to treatment, duration of illness prior to serum therapy had been from three to twelve weeks. Four of these relapsed after the initial course of serum treatment. These patients became afebrile in an average of nine days (three to twenty-one days), asymptomatic in an average of fifteen days (seven to forty-two days), able to resume their work in an average of three and one-half weeks (eight days to two months) Inadequate dosage, insufficient potency, too narrow valence, and too great chronicity may have accounted for their few failures Cases of over five months duration were unlikely to yield to serum therapy.

Later Foshay[254] used either goat or horse serum in patients whose illness prior to treatment did not exceed eight months (preferably not longer than five months). The average dose for moderate and severe infections in the adult was 60 cc. given in

three daily intravenous or intramuscular injections of 20 cc. each or in two daily injections of 30 cc each; for cases of unusual severity doses of 90 to 120 cc were recommended, in units of 30 cc. during a period of forty-eight to seventy-two hours. For children up to 13 years of age, with illness of average severity, a total of 20 to 30 cc. was usually sufficient. He did not recommend further administration of serum for the febrile relapses that occasionally followed Results in the treatment of 153 patients showed 4 failures, including 2 fatalities. Periods of observation were from six months to six years.

The majority of attempts to treat chronic brucellosis of more than eight months duration resulted in failures to obtain permanent recoveries although transitory immediate improvement was noted, lasting for from a few weeks to several months or even a year, with almost invariable return to the original state. Serum was especially valuable in the occasional severe acute exacerbation due to regional localizations during long-continued chronic infections In these instances he recommended 90 to 150 cc. or more of serum, followed by use of other methods more appropriate for the chronic form, as soon as immediate recovery permits.

In 1946 Foshay [237] stated that a postrecovery study of nearly 250 patients for a period of from four to fourteen years following treatment of acute brucellosis with antiserum showed a relapse rate which was "gratifyingly low" This is to be the subject of a formal report by him.

Beattie and Rice [46] reported successful use of the serum in 3 patients. Carpenter and Boak [120] treated 2 patients with bovine antiserum, with apparent cure in 1 and failure of improvement in the other A case of *Brucella abortus* infection in a 24-year-old patient treated with Foshay's antiserum was reported by Bannick and Magath [47] Response to four doses of anti-brucellosis serum given on four successive days was dramatic. Temperature became normal on the fifth day The liver and spleen rapidly diminished in size and the patient felt well. However, on discharge from the hospital, two weeks after admission, blood culture was still positive as it was again about five weeks later, at which time there

was a temporary recurrence of fever but without clinical symptoms. The authors were impressed by the prompt antitoxic effect of the serum.

An *anti-abortus* horse serum was prepared by Mitchell, Humphreys, and Walker[492] and used in 28 cases, with failure in 6.

Flippin[224] reported the treatment of 5 cases of febrile illness with a commercial anti-*melitensis* serum (Sharp & Dohme) in 1938. All had negative blood cultures and positive agglutination tests. All recovered within two to three weeks and remained well for periods of observation ranging from eight to twenty-four months. Duration of illness had been from one to thirteen months prior to treatment. Dosage consisted of 1.0 cc. of the serum intramuscularly as a test dose, followed in twenty-four hours, if no reaction occurred, by six daily intravenous injections of 50 cc. of serum, in 100 cc. of physiologic saline. The serum was prepared by inoculation of separate groups of cows with heat-killed *Brucella abortus* and *melitensis* organisms, the sera being then pooled. In 1946 Flippin[226] stated that 3 of these patients still were in good health; the other 2 of them had not been heard from for several years.

It is apparent that anti-*Brucella* serums have definite merit, at least in terminating the acute illness, in a large percentage of cases. Relapse may not be prevented.

The importance of observing the patient closely following remission is obvious. Unless a high phagocytic response is achieved and maintained for a period of years, production of active immunity through use of a suitable *Brucella* antigen is advisable.

Brucella Antigen Therapy

Until it can be demonstrated that *Brucella* organisms can be eradicated from the body by some uniformly effective and relatively innocuous means, use of some form of specific antigen must remain a basic or adjunctive method in the chronic illness.

The aims in *Brucella* antigen therapy are, (1) to induce immunologic response to aid the natural defense mechanisms in

combating infection, and (2) to bring about desensitization to *Brucella* organisms in order to lessen or remove allergic response, whether or not infection persists. Usually these aims are accomplished simultaneously. The means of attaining these ends have varied in the hands of different workers. The mechanisms involved are imperfectly understood.

ROLE OF ALLERGY AND IMMUNITY

Seegal[618] stated that the stimulating agent is highly complex in bacterial allergy and may be widely disseminated. The host's tissues are in an abnormal state of activity as a result of the infection. Manifestations of allergy in infection are therefore varied Immediate and delayed skin reactions as well as focal and general reactions may occur. Some of the histopathology in chronic infection may be the result of allergic inflammation She remarked: "The newer methods of immunochemistry which make possible the antigenic analysis of bacteria, the association of one fraction with virulence, the quantitative estimation of antibodies and an analysis of types of reaction between antigens and antibodies are certain to give impetus to the analysis of immunity and allergy . . yet it has more than academic interest for chronic diseases in which allergy may play such a significant role are often among those as yet uncontrolled by the chemotherapeutic agents."

The theory that improvement depends on the maintenance of a state of hypersensitivity[351] apparently in turn is based on the concept that an accelerated and exaggerated hypersensitive reaction inhibits the spread of bacteria and that hypersensitivity and acquired resistance parallel each other According to Aikawa,[4] it was once thought that hypersensitivity was responsible for the increased resistance acquired during infection He quoted Rich[571] as having shown evidence that the spread of bacteria is actually accelerated rather than retarded in the hypersensitive animal and that in no case does the hypersensitive reaction protect the animal from a fatal outcome Rich stated that in the immunized body, immediate immobilization of the bacteria is accomplished

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plish the desired end results most readily. The use of Brucellin is based on the maintenance of a high degree of sensitivity throughout treatment so that sharp allergic reactions are produced by each dose, no effect being expected in the absence of hypersensitivity. The aim is a polymorphonuclear and phagocytic response. Only hypersensitive patients may be treated effectively by this method.[351] Use of subtolerance dosage, with minimal or no allergic reactions, allows treatment of patients whether anergic or allergic to *Brucella* organisms or their fractions. It is difficult to reconcile the methods.

A possible explanation is that either approach, i e , desensitization through subtolerance doses or creation of hypersensitivity through sharp systemic febrile reactions, may ultimately result in desensitization and immune response. Even if this hypothesis is true, it must be considered that the subtolerance dosage of vaccine has certain definite advantages in that, (1) it is not attended by physical discomfort, (2) the patient may remain ambulatory and need not interrupt his daily routine, (3) he is much more likely to adhere to a regimen which is so easily borne and which may be reinstituted if relapse occurs, and (4) it is not attended by the possible danger from shock reactions and irreversible tissue changes. Since results are at least as favorable when these principles are employed, other measures are not recommended except under special circumstances. Leon and Sosa[435] stated, in agreement with Castaneda,[181] that all cases of brucellosis that are desensitized improve, and that most recover within two to five months of treatment.

patients that changes in allergic reactions to various foods and other allergens have been brought about fortuitously through the use of *Brucella* vaccine. Two instances of solar sensitivity in patients who were also sensitive to sulfonamides were reversed so that the patients were able to tolerate sunlight or sulfonamides following *Brucella* vaccine therapy for chronic brucellosis. Coca

by the action of the antibody, which causes the bacteria to adhere to each other and to the tissues where they lodge, and that immobilization has no relation to hypersensitivity. *He further stated that there is no parallelism between immunity and hypersensitivity—rather, that immunity is somewhat inversely proportional to the intensity of the local allergic reaction.* On the other hand, Rich also stated that no one has produced hypersensitivity without producing immunity. Aikawa concluded that, "confusion still exists regarding the relationship of immunity to hypersensitivity." This confusion is reflected in the various methods of antigenic treatment of brucellosis.

Dustin and Weyler[166] considered the relationship between chronic brucellosis and personal and familial allergy to be significant. Of the several hundred patients studied, 92 per cent had a history of allergy and all had a history of allergy in their immediate families. The clinical behavior of these patients, under treatment, indicated an allergic state rather than one of lowered resistance Darley and Gordon[162] saw no likely relationship between personal or familial allergy and sensitization to *Brucella*, and the symptomatology of chronic brucellosis. Whether or not personal or familial allergy plays a role in susceptibility to *Brucella* infection, the existence of allergies other than to *Brucella* may play an important part in rendering desensitization more difficult

It might be argued that it is of little moment whether symptoms are of purely allergic origin or due to infection plus allergy, since desensitization as well as immunologic response in the chronic illness is necessary in any event. There would, however, be different aims in treatment if allergy alone were to be considered. Under such circumstances there would be no need for aiming at immunologic response or of the frequent (and often fruitless) search for localized infection The distinction therefore has practical, as well as scientific, importance

Avoidance of any but minimal allergic reactions (except under special circumstances to be discussed) has seemed to conform most nearly to established immunologic principles and to accom-

cytic, response may lie in the degree of activity and localization of *Brucella* infection and the degree and localization of tissue sensitivity.

Meyer and Eddie [434] stated that "infection alone creates cutaneous allergy while vaccine injections merely stimulate the appearance of serum antibodies." This observation, if confirmed, would have practical importance in that intradermal reactions could still be viewed as significant in patients previously skin tested or treated with intramuscular or subcutaneous injections of killed organisms or their fractions Leon and Sosa,[435] however, stated that laboratory animals may be actively sensitized either with dead or living *Brucella* suspensions Somewhat in agreement with this finding are some unpublished observations of the author suggesting that cutaneous allergy may at least be enhanced in pa-

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from contact with diseased tissues, or from ingestion or inhalation of the organism, alive or dead, or from the ingestion of sterile broth filtrates on which the organism has grown He stated that the specific allergen must pass through the epithelium of the skin, the respiratory tract, or the digestive tract but that killed as well as live organisms in food will produce a reaction quite similar to those seen in chronic brucellosis. The opinion was expressed that "it is now a well-established fact that many cases of *Brucella* allergy have been and are constantly being mistaken for chronic brucellosis " Such a concept includes the possibility that use of pasteurized milk or other dairy products containing killed *Brucella* organisms may produce initial sensitivity or continued resensitization regardless of treatment. It could explain the tendency of brucellosis (or symptoms referable to *Brucella* allergy) to recur even in individuals who have been successfully treated

It is notable that the distinction between allergy and infection is clearly made. It is not clear how infection with consequent

pointed out that there is plenty of precedent for this observation in the similar effect of the injection of mixed bacterial vaccine and of tuberculin. He pointed to many instances of "food allergic" bronchial asthma who were freed of symptoms through use of nothing but mixed bacterial vaccine. On this basis it is conceivable that a small proportion of patients recover from *Brucella* allergy through use of nonspecific vaccines

Darley [161] emphasized the generally accepted view that *Brucella* sensitization is not synonymous with active *Brucella* infection. Discussing this controversial subject from the standpoint of tuberculosis, Meyers [508] stated: "How long allergy persists in a given individual after all tubercle bacilli have died is unknown. *Some believe that the reaction vanishes after one or two months;* others contend that enough protein is eliminated from dead bacilli up to two or more years to produce a response. During this time there is a gradual waning and a reaction to tuberculin may scale down to 1 plus, and then disappear. Therefore, with the exception of this interval, while sensitivity is waning and vanishing, and until all tubercle bacilli are dead, the tuberculin reaction always indicated the presence of living tubercle bacilli in the body of the reactor."

In some patients diagnosed as having brucellosis the manifestations apparently are on an allergic basis, with no demonstrable evidence of active infection. However, the absence of latent infection which may be responsible for the allergy cannot be proved. Some patients recover without significant phagocytic response, through desensitization In the majority, phagocytic response is an important criterion of recovery, relapse occurring whenever phagocytic activity lessens appreciably (p 408) The question has often arisen as to why it is not a uniform criterion. Some have pointed to the lack of uniformity of the role of phagocytosis as evidence of its unreliability. Others [351] have considered that some patients are suffering from *Brucella* allergy as distinguished from *Brucella* infection (p 459). It is reasonable to assume, (1) that *Brucella* allergy is primarily due to *Brucella* infection, and (2) that the difference in clinical, as compared with phago-

sensitization and the usually concomitant production of immunity. However, failure of recovery through desensitization, or recurrent illness in the presence of poor immunologic response, must lead one to consider the problem in the usual way, that is, to search for localized areas of *Brucella* infection

In several patients suffering from *Brucella* allergy, with no demonstrable evidence of active infection, cessation of all symptoms has followed treatment with streptomycin and sulfadiazine combined, thus strengthening the evidence that *Brucella* allergy is dependent upon continued *Brucella* infection

TYPES OF BRUCELLA ANTIGENS

Wright [727] pioneered the vaccine therapy of brucellosis, making the first report on the use of heat-killed *Brucella melitensis* organisms in 1905 *Brucella* antigens of many types have been used (See pages 467–474.)

Heat-killed or chemically killed mixtures of *Brucella suis* and *abortus* or of *melitensis* and *abortus*, consisting of from 1500 million to 6000 million organisms per cc., are commercially available from various manufacturers of biologic preparations.[493]

Heat-killed *Brucella abortus* vaccine was originally prepared by the New York State Department of Health, Division of Laboratories and Research, from culture No 322 isolated from a human case of brucellosis It is now available commercially (Sharp & Dohme).

Detoxified *Brucella* vaccine (formaldehyde-killed *Brucella abortus* and *suis* organisms partially oxidized with nascent nitrous acid) was originally available from the laboratories of Dr Lee Foshay of the University of Cincinnati, Ohio, but has not been made commercially available.

Autogenous vaccines made from heat or chemically killed *Brucella* isolated from the individual patient are prepared when there are special indications

"Lysed" vaccine was prepared by Caronia,[125] by incubating a saline suspension of *Brucella* with human anti-*melitensis* serum.

allergy, or allergy due to subclinical infection, perhaps increased by contact with live organisms (as in veterinarians), can be distinguished from simple *Brucella* allergy without *Brucella* infection, if indeed such exists. Huddleson stated that the results of a suitable allergic skin test and the opsonocytophagic power of the blood, when considered together, may furnish the necessary information in a majority of cases. Since a very low (so-called negative) phagocytic index may be found in the presence of active infection, and is always found in the absence of infection; since a positive allergic cutaneous reaction is said to occur either in the presence of *Brucella* infection or *Brucella* allergy, and since agglutinins are known to be frequently absent even in the presence of positive culture, these tests obviously cannot be relied [illegible]

[illegible]

it the clinical picture of *Brucella* allergy is quite similar to that seen in chronic brucellosis

It is the author's concept that allergic manifestations do not occur except in those who have been rendered hypersensitive to *Brucella* through infection at some time and that the burden of proof that the patient is not still infected rests upon the physician Whether infection persists in granulomatous tissue or whether the organism maintains an intracellular life is immaterial from the standpoint of allergy (although very important from the standpoint of eradication of infection) *Brucella* infection is too well known as a chronic, often ineradicable, infection to accept the theory that infection has disappeared and that allergy alone exists or persists indefinitely.

Tissue immunity, i e, immunity developed by cell and body fluid activity other than by antibody participation, in all probability plays a large although undefined role. It may account for many of the immunologic paradoxes encountered in the diagnosis and treatment of brucellosis

Whether or not *Brucella* allergy is due to infection (active or latent) or to ingestion of killed organisms the practical approach to treatment by means of *Brucella* antigens is the same, i.e, de-

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"M.B.P." is prepared in Mexico by Castaneda and his associates from the soluble fractions of partially ground *Brucella abortus, melitensis,* and *suis* organisms, in equal parts. It is available in Mexico from Oficio Farmacéutico Mexicana, S.A., Av. Chapultepec Nos. 151–153, Mexico, D.F.

Brucellin is a culture filtrate of all three strains of *Brucella* originally made at the Central Brucella Station, Michigan State College, East Lansing, Michigan, now produced by Sharp and Dohme.

Bacterial antigen complexes (B.A.C.-Hoffmann)[340] are prepared from each species of *Brucella*, by precipitation of proteins and exotoxins of bacterial filtrates by benzoic or salicylic acid.

GENERAL TREATMENT CONSIDERATIONS

Whatever the type of *Brucella* antigen employed, adaptation of the method to the patient is of vital importance. Many unfavorable results have followed injudicious use of some of these methods, particularly when obviously undesirable reactions were ignored.

The following excerpts from a letter written by one patient to another, both under treatment for brucellosis in distant cities, illustrate improper use of *Brucella* antigen

> Dr ——— began giving me the vaccine shots, finally, almost 9 weeks ago and I had seven of them and was hoping so much that they would help But unfortunately I developed a blood clot on my right hip, I noticed that I had an awfully big lump—big as an egg—but I thought every one did have, so didn't mention it until I had a highly excruciating pain in my right hip joint, about four to five weeks ago, and a huge swelling, big as the open hand The doctor was disturbed, and after trying it in each arm decided to stop it He said my muscles didn't react properly The blood clot, instead of being absorbed, has been all these weeks working to the surface, and will have to be opened up in a few days

Physician and patient shared the responsibility for this unfortunate result Had the patient complained of the marked local reactions, much greater dilutions of vaccine should have been

used or that method of treatment abandoned Had the physician inquired about reactions, they would have been discovered before sensitization had reached the point resulting in sterile abscesses.

Similar experiences are not uncommon Sensitization and lack of phagocytic response, with clinical failure, have been noted in many patients in whom the principle of desensitization with subtolerance dosage has been ignored When induration occurs at the site of the inoculation and fails to absorb within two or three days the indication for smaller dosage and usually for greater dilution is definite Cystlike areas of necrosis (sterile abscesses) are absolute contraindications for continued treatment with similar doses Under these circumstances there is rarely a satisfactory phagocytic response. If desensitization cannot be accomplished by use of greater dilution or a more suitable antigen it usually can be by intravenous administration (p 481).

Reactions similar to vaccines employed in other infectious diseases apparently have been expected by physician and patient This may account for the fact that reactions to *Brucella* vaccine so frequently are not recognized or are ignored. One physician who had treated more than a hundred patients stated that in no instance was dilution of vaccine necessary for no reactions occurred In the author's experience stock vaccine, even of the single strain *abortus* variety, must be used in dilutions of from 1 10 to 1 1000 or even greater, in at least half of the patients treated, in order to avoid undesirable and even deleterious effects (p 475).

Doubt as to the efficacy of any *Brucella* antigen remains in the minds of some,[118] in the face of impressive evidence of lasting recovery in many thousands of patients. Whereas healthy skepticism is justifiable concerning the treatment of any illness which may be self-limited, it is frequently forgotten that an unfortunately large percentage of *Brucella* infections are limited only by the lifespan of the patient It is in these patients who have remained ill or who have repeatedly relapsed, year after year, that the efficacy of antigenic therapy has been demonstrated

Carpenter and Boak,[120] in a review of treatment methods,

enumerated 325 cases, reported by various authors, in whom marked improvement or cure was apparently attributable to *Brucella* vaccine of various types, and only 18 cases in which results were unsatisfactory. They were particularly impressed by the results of use of a lysed vaccine in 66 cases,[125, 138, 165] stating that "usually a slight febrile reaction occurred after injection of the vaccine," and that "the brilliant results . . . in 66 cases without a single failure, should prompt others to employ it." Many favorable reports were cited,[19, 42, 520, 536, 627] and others equally favorable were omitted.[177, 209, 627] Yet they arrived at the conclusions that, (1) all treatment methods evoke a systemic reaction and that this reaction is responsible for the beneficial results, and (2) that no therapeutic agent had yet been found which had been proved to alter, to a significant degree, the natural course of the disease.

There is ample evidence that *Brucella* antigens, when carefully chosen and properly used, in accordance with the tolerance and response of the individual patient, bring about favorable changes in the course of the chronic illness. No review of the literature can substitute for prolonged experience with large numbers of patients

THERAPEUTIC TRIAL OF BRUCELLA ANTIGENS

Whereas the indiscriminate use of *Brucella* vaccines or related antigens is to be avoided, their therapeutic trial in patients properly suspected of *Brucella* infection is as logical as therapeutic trial in the treatment of other conditions The intradermal reaction alone as an evidence of active brucellosis is indeed meager but occasionally, in a patient with a definite history of exposure or a past history indicating brucellosis (with existing symptoms which are strongly suggestive of brucellosis), such tenuous evidence may have to be considered *The hasty performance of a skin test, with omission of complete study to establish or rule out other diagnoses, and without use of the other tests for brucellosis, is not an adequate basis for diagnosis or treatment.*

In only one instance was therapeutic trial of *Brucella* vaccine used in the absence of any laboratory evidence of brucellosis. The possibility of *Brucella* infection was suggested in this 50-year-old woman by the presence of an intractable periarthritis of the shoulder with intense pain of six months duration, the history of ingestion of raw milk and cream from her husband's herd, known to be grossly infected, and the fact that similar pathology had existed in other patients known to be infected. Blood-agglutination and intradermal reactions were negative and the opsonocytophagic test noninformative In spite of the absence of any skin sensitivity this patient responded to the first intramuscular dose of *Brucella abortus* vaccine, given at her own request, with an unexpected local, focal, and systemic reaction involving various joints After adjustment of dosage and dilution of vaccine to avoid further reaction there was clinical recovery, with a marked rise in the phagocytic power of the white cells.

It is to be expected that errors in diagnosis will often be corrected through therapeutic trial of vaccine Failure of clinical response to treatment, in the presence of good serologic response, should lead to reconsideration of diagnosis and search for possible localized infection

INTRADERMAL ADMINISTRATION OF ANTIGEN

Intradermal injection of vaccine may accomplish desensitization and immunologic response with clinical recovery in some patients more rapidly than by other routes This response was noted accidentally in several patients who reported rapid clinical response following skin-testing doses of *Brucella abortus* vaccine In all such instances there was a commensurate increase in phagocytic activity, even to high levels, within as short a period as six days In some patients both the phagocytic and clinical response was of long duration (in one patient five years) so that no treatment seemed indicated.

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tion have been noted following violently reacting intradermal reactions. Griggs[241] expressed the belief that persistence of sensitization, which he very frequently encountered, may be due to more or less permanent skin changes at the site of violently reacting intradermal inoculations. Complete refractoriness to desensitization over a period of more than a year occurred in only 3 of the author's patients In other patients following violent intradermal reactions persistence of hypersensitivity and of the refractory stage was of only a few weeks duration. In some, cautious use of dilute vaccine intramuscularly hastened desensitization and resolution of the healing, necrotic skin-test site; in others there was exacerbation of skin necrosis and undue systemic reaction, necessitating temporary cessation of treatment.*

Urschel[676] stated that this improvement after skin tests has been frequently observed, and that it occurs in patients who have no knowledge as to what skin tests had been done. The psychologic factor can be quite certainly excluded, especially in view of the commensurate phagocytic response so often noted.[301] Also in agreement with Urschel's observations, it has been noted that the clinical and serologic response to skin-testing doses of vaccine may be fleeting

The improvement following a strongly reacting intradermal test was so marked as to cause one patient to return five years later, requesting "another skin test for brucellosis." He had been entirely free of symptoms for nearly five years after an initial skin test, after having been ill intermittently for nearly fifteen years prior to the diagnostic test He showed an equally satisfactory clinical and serologic response to the second intradermal dose

The intradermal route of administration of *Brucella* vaccine has seemed less dependable and satisfactory in clinical and phagocytic response than the intramuscular route, in a small number of the author's patients Urschel[675] considered his results in 28 patients with chronic illness treated by the intradermal route superior to that obtained by subcutaneous injections. Later he re-

* Desensitization, with rapid healing of these necrotic reactions, may follow use of aureomycin or chloromycetin.

ported[619] apparently good results in 4 acutely ill patients by the use of dilute *Brucella suis* and *abortus* mixed vaccine, with less likelihood of severe systemic reactions and with smaller dosage. It is felt that the systemic disturbances can be controlled equally well if dosage and dilution by the intramuscular route is adapted to each patient's tolerance.

VARIOUS TECHNICS OF ANTIGEN THERAPY

Mixed Strain Vaccines

Mixed strains of *Brucella* organisms (*suis* and *abortus*) have been used with favorable response in from 60 to 85 per cent of patients by Simpson,[632] Angle,[19, 22] and others.

Angle used 0.25 cc. of a stock suspension containing 3000 million each of killed *suis* and *abortus* organisms per cc. Initial dosage was 0.25 cc. every second or third day. Dosage did not exceed 1.0 cc. He considered it important to avoid overtreatment, usually giving not more than seven injections during a single course.

Simpson[632] pointed out that better standards for preparation of vaccines have been employed in recent years, both in choice of suitable strains and concentration of vaccine. He advised use of the *melitensis* strain only in *melitensis* infections, using vaccine composed of *suis* and *abortus* strains in equal quantities routinely. He described the following technic.

> To test for hypersensitivity, 0.05 cc. of a 1:10 dilution of the vaccine is injected intracutaneously. If there is no excessive local or systemic reaction within forty-eight hours, 0.25 cc. is given deep into subcutaneous tissues or preferably intramuscularly. This is followed by a second dose of 0.25 cc. three days later if there has been no untoward reaction and then by subsequent doses in increments of 0.25 cc. at three-day intervals until a dose of 1.0 cc. is reached. Five to 8 injections of 1.0 cc. may then be given at three-day intervals. Dilutions of 1:10 or 1:100, with increments of 0.1 cc. were advised in highly sensitized patients with reduction in dosage to one-half the previous amount and then cautious increase if unusually severe local and systemic reaction should occur. A series of 4 to 6 or more sharp systemic febrile reactions, usually accompanied by a transient exacerbation of

tion have been noted following violently reacting intradermal reactions. Griggs[281] expressed the belief that persistence of sensitization, which he very frequently encountered, may be due to more or less permanent skin changes at the site of violently reacting intradermal inoculations. Complete refractoriness to desensitization over a period of more than a year occurred in only 3 of the author's patients. In other patients following violent intradermal reactions persistence of hypersensitivity and of the refractory stage was of only a few weeks duration. In some, cautious use of dilute vaccine intramuscularly hastened desensitization and resolution of the healing, necrotic skin-test site; in others there was exacerbation of skin necrosis and undue systemic reaction, necessitating temporary cessation of treatment.*

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for a month. Results were "not inferior to those obtained with other vaccines," at least one-half of the patients recovering, one-third being markedly improved, and 11 to 18 per cent not improved. He warned against overdosage and the almost invariable fall in phagocytic activity which followed. The phagocytic tests, performed once each month, were found to be the best index of proper dosage and duration of treatment. Foshay expressed the opinion that *melitensis* strains should be restricted to patients infected with that strain, to avoid a state of refractoriness which often follows its use.

Calder [203] reported the results of treatment with this detoxified vaccine in 140 patients, stating that fever persisted in 6 per cent of the cases and inadequate opsonins were found in 6.6 per cent after twelve months of treatment, leading him to classify them among the therapeutic failures. Among those improved he found that fever disappeared in an average of two and seven-tenths months and that satisfactory phagocytic response was achieved in an average of four and a half months. Since these patients had been ill for an average of forty-five months the possibility of coincidental spontaneous recovery seemed remote. Foshay considered that the probability of future relapse is not greater than 1 in 10 patients if vaccine is continued until 80 per cent or more of the white cells show marked phagocytosis.

Moss [493] reported excellent results in over 90 per cent of 74 cases of chronic brucellosis, using this antigen.

Lysed Vaccine

Caronia [125] prepared a vaccine by incubating a saline suspension of *Brucella* with human anti-*melitensis* serum for thirty-six hours at 37° C., addition of more antiserum, reincubation for another thirty-six hours, addition of 0.5 per cent phenol, slow centrifugation, and heating of the supernatant fluid for 1 hour at 55° C. on three successive days. He reported its successful use in 1917 in 8 patients after two to five intramuscular injections of 1.0 cc. of the vaccine. Chiriaco [138] treated 3 patients with satisfactory results and DeFinis [265] reported the cure of 55 cases using this method. DeFinis reported immediate improvement following

symptoms, is the aim of treatment, with avoidance only of extreme local or general reactions. Febrile response from 103 to 105° F. is not uncommon from initial or subsequent doses. In chronic brucellosis larger doses may be required; if no reaction is provoked after 5 to 6 injections of 1.0 cc each, the dosage may be gradually increased by 0.5 cc. increments to 2.0 or 3.0 cc.

He did not use the opsonocytophagic test as a guide to therapeutic response because of inconsistent results in his experience with it. Sterile abscesses are not uncommon under this regimen.

Detoxified Brucella *Vaccine*

Detoxified (nitrous-acid-treated) strains of *Brucella abortus* and *suis* were reported [103, 234, 520] to have produced successful results in a large number of patients observed over long periods of time. Reactions were avoided in employing this vaccine.

Calder,[103] noting that if *melitensis* strains were included in the vaccine, agglutinins rose to high titers, opsonins decreased, and clinical results were poor, used only the *abortus* strains in his patients in Texas where *suis* infections were rare. Vaccine was given daily, subcutaneously, in amounts to approach but not to exceed the allergic tolerance. Erythema of more than one inch diameter, induration, swelling, or excessive local pain served as an indication for reduction of the dose; otherwise daily increments were 0.02 cc. Treatment was discontinued when a high opsonic level was reached. There was close correlation between opsonic and clinical response.

Foshay [234] varied the initial dose of his vaccine according to the sensitivity of the patient, usually giving 0.05 cc. of a strength of T-100 (approximately equivalent to a density of 200 million organisms per cc.), maintaining the dose for ten days, then gradually increasing by increments of 0.05 cc. to 0.1 cc., giving at least four doses at each new level before again increasing. Dosage rarely exceeded 0.5 cc. and was given subcutaneously six times weekly. Dilutions were increased to T-25 (a 1:4 dilution of T-100 density) or lower density when necessary to suit the patient's tolerance. Treatment was stopped when the phagocytic index had reached and maintained a numerical level of 80

Thirty-five patients, 20 of whom yielded *Brucella melitensis*, were treated, 4 classed as mild illnesses, 25 as severe, and 6 as grave In the mild cases improvement was noted in nine, twelve, and forty-five days and they continued to improve for twenty-nine, thirty-seven, fifty-one, and one hundred and five days, respectively, following which complete recovery was established They were all considered to be *Brucella melitensis* infections In the 25 severe cases recovery began in from three to sixty days after treatment was begun Treatment was continued for from one to four months.

In the 6 cases classed as grave, improvement began in a relatively short time. Two of them were given anti-*melitensis* serum to tide them over the most severe stage before vaccine was given One was given several transfusions and parenteral liver extract because of a grave secondary anemia and severe purpura. The 3 others received vaccine only. Four were discharged as cured, 1 recovered, 1 as "entirely well" The period of treatment and observation varied from one to seven months.

They pointed out that their results were not as striking as those reported by some others but that a rapid and sustained improvement without severe reactions occurred, and without mortality in even those gravely ill

D'Antoni[157, 158] reported extensive use of this vaccine, stating that his results over a period of four years had been excellent Castañeda's antigen has been used by the author in 34 low-grade chronic infections with good clinical and serologic response in the majority It may be effective in patients who are refractory to *Brucella abortus* vaccine treatment Its use in the usual concentration is apparently seldom attended by marked reactions However, violent reaction occurred following its use in a 1 10,000 dilution in one hypersensitive patient

Brucellin

Brucellin affects the course of the disease by producing a systemic allergic reaction which in turn is accompanied by a neutrophilic leukocytosis and increase in immune opsonins, its efficacy is stated to depend upon the continued existence of a state of sensitization in the patient throughout treatment, desensitization is scrupulously avoided, such a state rendering subsequent doses ineffective.[851]

its use, with defervescence of fever by crisis or lysis and rapid return to normal of enlarged livers and spleens.

Autogenous Brucella *Vaccine*

Autogenous *Brucella* vaccine treatment is possible only in the presence of positive culture and is therefore not applicable in the majority of chronic illnesses. Foshay [234] considered it preferable to use an autogenous vaccine made from the patient's infecting strain, whenever possible, either alone or in combination with other strains of the same variety, preferably those that have been isolated from man or animals in the same geographic region, because of the variation in antigenic structure in different strains. There are few references in the literature to autogenous vaccine, most of those referring to only a few cases. Owen and Newham [524] reported the successful treatment of 1 patient; Courcoux, Lelong, and Cordey [147] the unsuccessful treatment of 9 cases, Schilling, Magee, and Leitch [603] the successful treatment of 1 patient, and Hansmann and Schenken [288] the fatal termination in a case of *Brucella* meningo-encephalitis. Poston and Smith [570] reported the use of an autogenous *Brucella* vaccine in what may have been a successful attempt to prevent relapse following recovery from *Brucella* meningitis

M B P (Castaneda)

Castaneda and Cardenas [110, 112] prepared an antigen from soluble fractions of partially ground *Brucella abortus, melitensis,* and *suis* organisms, in equal parts.

Their usual routine was to begin treatment with 0 2 cc. given intradermally, to determine the allergic state Subsequent injections were given twice weekly, subcutaneously, in gradual increments but not exceeding 2 5 cc The dosage was varied with the reaction produced A rise in temperature of over 1° C. above the previous day's maximum was considered a contraindication to an increase It was not given if temperature was over 40° C Their aim was to produce only mild or no reactions, to desensitize, and to increase immune resources

at least six months. It was said that relapses could be prevented even though the patient remains infected.

Contraindications were listed as. cardiac diseases, brain tumor, pernicious anemia, aplastic anemia, epilepsy, and diabetes.

The author abandoned the use of Brucellin in favor of subtolerance doses of *Brucella abortus* vaccine in 1934 because of the usual severity and occasional violence of reactions and the less favorable clinical and immunologic response. In one patient a severe hepatitis and icterus followed its use, in another a severe nephritis Several patients who reported good responses to Brucellin had had modified dosage so as to avoid the sharp febrile reactions.

Benning[278] reported on the use of Brucellin in 97 patients in 1946 with improvement in 89.7 per cent of 78 cases which were followed for six months or more. Borts and his coworkers[74] reported the use of Brucellin in 77 persons acutely ill with *Brucella suis* infections which occurred in epidemic form. The average number of injections was fifteen. Three of the patients reacted with extreme elevation of temperature and exhaustion following the initial dosage and the use of Brucellin was discontinued. These patients were given sulfathiazole with satisfactory response and recovery.

Bacterial Antigen Complex (Hoffmann)

Because no antigen has been found that will bring about desensitization, immunologic response, and lasting recovery in all *Brucella* infections, bacterial antigen complex made from the three separate strains of *Brucella* (p 462) is under investigation

A total of 98 patients are under treatment, or under observation following treatment, by this method, all except 2 in the chronic phase of the disease. Although it is too early to draw definite conclusions, the method gives promise of effectiveness in comparatively rapid desensitization and immune-body production. Among the first 43 patients treated, 40 were markedly improved or apparently recovered Desensitization with one of the *Brucella* B A C. preparations proceeded smoothly in 4 patients with ex-

It is administered as follows:

In the acute illness, an intradermal injection of about 0 1 cc. is given to determine the sensitiveness of the patient. If there is no marked systemic reaction within twenty-four hours, 0 5 cc. is given intradermally. This dose is repeated at three-day intervals until temperature remains subnormal between injections, providing that a systemic febrile reaction and local reaction is elicited from each dose. Usually three or more such reactions are induced. If there is not the expected local and systemic reaction to the first dose of 0.5 cc , the second dose is increased to 1.0 cc., part intradermally and part intramuscularly, this dose is then repeated if the desired reaction is obtained. If desensitization (failure of reaction) occurs during the course of treatment, an interval of ten to fifteen days is allowed to elapse and then treatment is resumed with 0.2 cc. to 0 5 cc. at fifteen-day intervals. Temperature is recorded morning and afternoon for at least fifteen days after treatment is discontinued in an attempt to determine relapse.

A group of 86 patients suffering from *melitensis* infection in Malta was studied; 28 of these were left untreated as controls Seven of the 58 treated cases were not influenced by treatment, the others showing symptoms for from three to twelve days after treatment was begun. Among the untreated controls 12 recovered within twenty days after admission to hospital and the other 16 still showed symptoms two months after admission Huddleson stated. "It has been the experience of physicians in Malta that a patient must be kept under observation for twelve to fifteen days after the temperature returns to normal in order to determine recovery Such a long period of observation * is necessary because of the occurrence of apyrexial periods during the course of the disease which very often lasts from six to twelve days. The cases in this study were kept under observation for twelve to fifteen days after the temperature became normal or subnormal Ten of the treated cases were questioned six months after treatment as to their state of health None reported a return of symptoms"

In the chronic illness, the same regimen was advised. About 25 per cent of cases will respond, the majority relapsing in fifteen to thirty days after the third or fourth injection These are treated with three reacting doses at three-day intervals, then at fifteen-day intervals for

* This period of observation is, of course, far too short

at least six months. It was said that relapses could be prevented even though the patient remains infected.

Contraindications were listed as: cardiac diseases, brain tumor, pernicious anemia, aplastic anemia, epilepsy, and diabetes.

The author abandoned the use of Brucellin in favor of subtolerance doses of *Brucella abortus* vaccine in 1934 because of the usual severity and occasional violence of reactions and the less favorable clinical and immunologic response. In one patient a severe hepatitis and icterus followed its use, in another a severe nephritis. Several patients who reported good responses to Brucellin had had modified dosage so as to avoid the sharp febrile reactions.

Benning[275] reported on the use of Brucellin in 97 patients in 1946 with improvement in 89.7 per cent of 78 cases which were followed for six months or more. Borts and his coworkers[74] reported the use of Brucellin in 77 persons acutely ill with *Brucella suis* infections which occurred in epidemic form. The average number of injections was fifteen. Three of the patients reacted with extreme elevation of temperature and exhaustion following the initial dosage and the use of Brucellin was discontinued. These patients were given sulfathiazole with satisfactory response and recovery.

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treme sensitivity who had reacted unfavorably *to any previous Brucella* antigen. *Phagocytic response was rapid in most patients* after four or more intradermal doses. In 5 patients clinical and serologic response was notable following the initial test doses only.

A treatment regimen which is apparently satisfactory is as follows:

The three bacterial antigen complexes, made separately from *abortus, melitensis,* and *suis* strains, are injected intracutaneously, in amounts of 0.02 cc. of each A similar amount of sterile physiologic saline is used as a control. Reactions are observed over a period of thirty minutes, and any urticarial reactions, pseudopodia, and erythema are recorded. Reactions are again noted and recorded at the end of twenty-four hours The B.A.C. causing the most definite immediate (or delayed) reaction is selected for initiation of treatment. When two or all three of the immediate reactions are similar in intensity, the reaction persisting longest is assumed to indicate the greatest sensitivity.

Subsequent dosage of the selected *Brucella* bacterial antigen complex is given, also intradermally, in increments of 0.01 cc., at intervals of four to seven days Systemic or focal reactions of more than minimal degree and twelve to twenty-four hours duration are considered indications for repetition of the previous dose or employment of a dilution of 1:10 or greater In hypersensitive patients dilutions of as much as 1:10,000 may be necessary to avoid undue reaction and to accomplish desensitization (A mixture of the three antigens has given more satisfactory response in recent experience.)

No firm criterion of duration of treatment has been worked out as yet. Treatment may apparently be stopped as soon as there is desensitization, immune response, and clinical recovery No patient has been observed longer than fourteen months.

Heat-killed Brucella Abortus *Vaccine*

Heat-killed *Brucella abortus* vaccine (bacterin) prepared from the organism isolated from the blood of a human case of brucellosis, and designated by the bacterial collection number 322, has

been used in at least 500 patients Periods of observation have been from one to fifteen years. The absence of *suis* and *melitensis* strains reduces its reaction-producing qualities with no apparent lessening in its value as a desensitizing and immunizing agent. It is applicable to most cases, except in the presence of severe toxic febrile illness, contraindications are few because reaction can be controlled Hypersensitivity, however, may be found even to great dilutions in the exceptional instance An advantage is the relative infrequency of dosage (usually four- to seven-day intervals) that is effective in most patients.

Khaled[839] apparently originated the theory that use of a heat-killed *abortus* strain would be less toxic than the *melitensis* strain in 1923 Although his own results were not impressive, the principle seems to have been correct.

Avoidance of local, focal, or systemic reactions, or production of fleeting minimal reactions only, has proved a successful method of concomitant desensitization and immunization The following principles, most of which apply to any antigen, have been employed

Sensitivity of the patient to Brucella abortus *vaccine*, if not already known from the degree of local, focal, and systemic reaction to a diagnostic skin test, may be determined by an intradermal injection of 0 1 cc of the vaccine When undue skin sensitivity is suspected, as in those occupational groups (laboratory workers, farmers, veterinarians, and slaughter-house employees) who have been exposed by direct skin contact to large numbers of organisms, or in the presence of central-nervous system or intra-ocular manifestations it is desirable to use dilutions of 1 10, 1 100, or 1 1,000 for initial skin testing, to avoid possible skin necrosis and undesirable focal reactions

Route of injection is preferably intramuscular, in alternate deltoids Subcutaneous injection is more likely to result in fat necrosis in sensitive patients and lesser immune response in most patients Intradermal and intravenous routes are discussed separately

The initial dose and dilution of vaccine is of importance since it may determine sensitization and, rarely, sterile abscess It usually should be withheld in the presence of a strongly or violently reacting

intradermal test, until reaction has subsided Intradermal reaction and sensitization may be increased by intramuscular injection if given too early. An initial dose of 0.2 cc. of the stock concentration of 2,000 million organisms per cc. may be given to the average patient whose skin reaction showed from 5 to 10 mm of induration. (In the exceptional instance a patient relatively insensitive to intradermal vaccine will react strongly to vaccine given by the intramuscular route) In the presence of a moderate reaction to the skin test, an initial dose of 0.2 cc. of a 1:10 dilution (200 million organisms per cc.) may be employed. Following a marked reaction to the intracutaneous test, an initial dose of 0.2 cc. of a 1:100 dilution (20 million organisms per cc.) will usually avoid untoward reaction. In the presence of a severe or *violent reaction to the intradermal dose of vaccine, a dilution of 1:1,000* (2 million organisms per cc.) or greater is indicated to initiate treatment.

Reactions of three types must be evaluated—local, focal, and systemic.

Local reaction may vary from only the fleeting soreness to a markedly swollen, hot, reddened area. Significance should be attached to the local reaction if it is marked, prolonged, followed by a subcutaneous fluctuant nodule, or accompanied by more than mild and fleeting focal and/or systemic reaction

Focal reaction may be of definite significance as a diagnostic aid and as an indication for the need for caution in subsequent dosage Increase in existing focal symptomatology, such as exacerbation of salpingitis, joint swelling and pain, lymphadenopathy and so forth, occurring within twenty-four hours after each of several doses of vaccine, usually can be interpreted as evidence that the focal pathology is indeed a part of or an allergic response to the infectious process. Such phenomena may be nonspecific in some instances Increase in neurologic or ocular signs or symptoms would constitute a danger signal unless followed by definite and demonstrable evidence of improvement (p 447)

Systemic reaction will usually accompany local or focal reaction or any type may occur independently of the others. If mild and not prolonged beyond thirty-six hours, it may be ignored,

especially if followed by an increasing sense of well-being, objective evidence of improvement, and a rising phagocytic index.

Severe reactions to intramuscular doses are to be avoided unless their incidental occurrence demonstrates their value. Rarely such unexpected reactions may be produced by accidental intravenous administration, even when the usual precautions against such occurrence are observed

A peculiar but not rare occurrence is sensitivity manifested by reactions to intramuscular injections in one deltoid muscle but not in the other. When encountered it should not be considered as coincidence or evidence of the patient's fancy, for objective evidence is present—local redness, swelling, and febrile reaction. This may occur whenever the "sensitive" deltoid is used for injection It may necessitate variation in dosage or exclusive use of the opposite arm or of the gluteal muscles

Subcutaneous nodules accidentally produced may be ignored if absorbed within a few days. If a subsequent vaccine injection is given while a local nodule reaction persists, even though reactionless, local tissue sensitivity may increase, causing marked sensitivity at the remote sites of previous inoculations, and the formation of sterile abscesses, which may drain spontaneously or require incision They are of unfavorable significance and their production should be avoided In some instances, long rest periods are necessary In others use of the cutaneous or intravenous route will rapidly desensitize

Dilutions of *Brucella abortus* vaccine may be kept on hand, properly refrigerated, for weeks or months Dilutions made by aspirating the stock vaccine preparation into a syringe and then aspirating sterile physiologic saline or sterile distilled water to the desired point are inaccurate, especially in the greater dilutions. Vaccine-type vials containing 10 cc of sterile physiologic saline solution, with rubber caps, are commercially available Removal of 1 0 cc. of sterile saline and its replacement with 1 0 cc of the stock vaccine preparation makes a 1·10 dilution Similarly, 1 0 cc of the 1 10 dilution in 9 0 cc. of sterile physiologic saline makes a 1 100 dilution Usually dilutions up to 1:1,000

suffice for even highly sensitive patients. Rarely a 1:10,000, *1:100,000, 1:1,000,000 or greater dilution may be necessary for* the initiation of treatment.

Interval between treatments may vary from four to seven days, depending upon the clinical and phagocytic response. An interval of seven days should not be exceeded in highly sensitized patients, greater sensitization may result.

Increments may vary from 0.05 to 0.15 cc., depending upon clinical and phagocytic response. Occurrence of more than a mild, fleeting local, focal, or systemic reaction is an indication for repetition of the previous dose; if reaction of any severity occurs, use of a greater dilution is indicated. If sensitivity persists, a rest period or intravenous administration may be indicated.

A course of treatment consists of whatever number of doses, of any dilution, are necessary to establish clinical and serologic response. Complete and lasting recovery may follow four to six doses. Occasionally complete clinical recovery, with marked phagocytic response, will follow the skin-testing dose of vaccine alone, precluding the need for treatment, temporarily or for an indefinite period (p. 466). Seldom need a maximum dose of 1.0 cc. of the stock vaccine be exceeded. A usual course of treatment consists of six to ten doses, but no standardization is possible. When treatment is begun with the more dilute preparations, progression through the lesser dilutions to full strength vaccine may be advisable, however, some patients respond to any well-tolerated and effective dilution. A small percentage of patients may require treatment intermittently over a period of many years, apparently often because of the existence of undiscovered or ineradicable foci of infection, or perhaps because of the persistent intracellular growth and multiplication of *Brucella* (p. 98). Sites of localized infection must be searched for and treated conservatively or surgically.

Criteria of progress are furnished by periodic redetermination of the phagocytic index, and other laboratory and clinical evaluation. In the majority of cases the rise in the phagocytic index will *closely parallel clinical response*, whereas a persistent fall

will usually presage relapse (p. 325). Achievement of a high phagocytic level (60 per cent or more cells showing marked phagocytosis or a numerical index of 80 or above) is not proof of recovery, in itself. Infection may remain active or allergic phenomena may persist (p. 458). Maintenance of a feeling of well-being, recovery of lost weight, and restoration of temperature, blood cells and sedimentation rates to normal levels, all are favorable indices

High phagocytic levels may accompany a continued state of sensitization, indicating the importance of desensitization An overwhelming infection may progress to a fatal termination in spite of very high phagocytic levels[579]

Complete recovery can be said to be achieved only if favorable response to treatment has lasted three to five years following cessation of treatment. Absence of symptoms referable to brucellosis may be a satisfactory status even in the presence of a steadily declining phagocytic index, on the basis of possible complete quiescence of infection or its actual eradication

Relapse of acute illness or recurrence of manifestations of chronic illness may occur needlessly if the phagocytic index is not used as an aid in assessing the patient's condition The following regimen is suggested· (1) repetition of the test at intervals of three or four weeks during the course of vaccine treatment, since it usually serves as a reliable criterion of progress, (2) performance of the test at gradually lengthening intervals after vaccine therapy is stopped, a definite decrease in the index on 2 successive tests will often presage relapse, pointing to the wisdom of resuming vaccine treatment.

Inhibition of phagocytic activity and/or resensitization may follow prolonged use of vaccine in an occasional patient Under such circumstances, discontinuance of vaccine therapy usually will result in a spontaneous return to the desired immunologic balance

Contraindications to *Brucella abortus* vaccine therapy are few if it is used in appropriate dilutions and amounts, at optimum intervals, and with due regard to the needs of the individual.

Usually it is not needed in the acute phase of the illness because of the efficacy of other methods. When indicated, it should be used with caution, in high dilutions at first, or the nitrous-oxide-treated vaccine or B.A.C. may be employed. Its use following remission of the acute illness may be of vital importance unless *a high phagocytic response has been achieved and maintained,* or unless it is felt that cure has been accomplished.

In the presence of central-nervous-system and ocular involvement it must be used with caution, in suitable dilutions to avoid possibly irreversible focal reaction. In one patient who previous to a meningo-encephalitis had received great benefit from vaccine, without reaction, there were unfavorable focal reactions to any dilution employed in the chronic illness which followed, with increase in neurologic signs, necessitating its abandonment. Ocular involvement is not a definite contraindication but a signal for cautious use to avoid focal reaction. Cases of iritis, keratitis, conjunctivitis, choroiditis, and retinitis have been treated with *Brucella abortus* vaccine, with results varying from spectacular to none.[305] *It is essential that there be close cooperation between the neurologist or ophthalmologist and the physician administering the vaccine.*

More than the usual precautions against reactions may be necessary under some circumstances such as auricular fibrillation The following is an example.

On August 18, 1946, a 51-year-old woman was seen during an attack of cardiac decompensation with auricular fibrillation With rapid digitalization there was restoration of normal heart action, diuresis, and subsidence of edema She then complained of pain and tenderness in the right ankle of several months duration and revealed a history of osteomyelitis of both femurs and tibiae of unknown etiology, thirty years before Radiographs showed a shadow suggesting a small collection of fluid in soft tissue overlying the malleolus but no evidence of bone disease

Routine tests suggested an old, probably still active, *Brucella* infection *Brucella abortus* vaccine was given on September 12, 1946. Although the intradermal reaction to the same vaccine had been mild,

she reacted unexpectedly to the intramuscular dose with fever, headache, malaise, and prostration The area of painful swelling disappeared within seven days but heart rate increased and dyspnea recurred. The second dose of *Brucella* vaccine was of a 1:1,000 dilution but also was followed by a febrile reaction with chest pain An electrocardiogram again showed long runs of fibrillation. Six days later heart action returned to normal and she had no further complaints Whether or not the heart condition was attributable to *Brucella* infection, it seemed certain that it was unfavorably affected by *Brucella* vaccine

Toxic effects from *Brucella abortus* vaccine used in proper dilutions are rarely encountered. In the presence of hepatitis a causal relationship may be suspected, although it is a fairly common finding in untreated cases. In only one hypersensitive patient was there reason to suspect that liver dysfunction was caused by toxic effects of *Brucella abortus* vaccine. There was prompt reversal to normal liver function following temporary cessation of vaccine. Resumption of vaccine a month later produced no further symptoms referable to the liver.

Intravenous administration of vaccine may be indicated in the presence of slow or unsatisfactory clinical and serologic response to *Brucella abortus* vaccine by the intramuscular route after a treatment period of from six to ten weeks Desensitization is likely to ensue rapidly. Reactions from this mode of administration are to be expected but their severity is seldom marked if graduated dosage is employed. For the average patient the following schedule usually is effective and well tolerated:

1st dose 0 05 (5/100) cc of a 1 1,000 dilution (100,000 organisms)
2nd dose 0 05 (5/100) cc of a 1 100 dilution (1,000,000 organisms)
3rd dose 0 05 (5/100) cc of a 1·10 dilution (10,000,000 organisms)
4th dose 0 05 (5/100) cc. of a full-strength vaccine (100,000,000 organisms)
5th dose 0 1 (1/10) cc of a full-strength vaccine (200,000,000 organisms)

This tentative schedule should be modified if reactions are very severe or prolonged If the temperature reaction following

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4th dose 0 05 (5/100) cc of a full-strength vaccine (100,000,000 organisms)
5th dose 0 1 (1/10) cc of a full-strength vaccine (200,000,000 organisms)

This tentative schedule should be modified if reactions are very severe or prolonged. If the temperature reaction following

any dose exceeds 103° F., if there is marked prostration without improvement promptly following, or if the period of reaction exceeds three days, the previous dose should be repeated. The use of vaccine should be abandoned or discontinued for from two to four weeks if there are two successive severe reactions. At the end of this period, if adequate clinical and serologic response has not become evident, intramuscular dosage may be resumed with reasonable expectation of favorable response.

Whereas the intravenous route in proper dosage is considered to be safe, it is recommended that treatment should not be initiated by this method in patients who have not received intramuscular doses within seven days, because of the unknown status of their sensitivity.

The interval between intravenous doses should not exceed seven days to avoid possible resensitization between doses The optimum interval is four to seven days

Clinical and serologic response is usually noted within four weeks following the intravenous course of vaccine.

The intravenous route has been employed in more than 100 patients since 1934 without ill effect, although its favorable effect has not been entirely uniform (it has failed in about 10 per cent of cases). It has been used by others since 1927. Bianchi [53] considered it the best method of therapy, quoting Cattaneo, DiGuglielmo, and others as having confirmed his results DiGuglielmo [177] was quoted as having employed this method in more than 130 cases, with recovery in all patients. He was so sure of its harmlessness that he used it at all ages from 4 to 77, and in all conditions, even the most grave, not excepting renal involvement. Fischera's good results in 9 cases and Grasso's report of the ambulatory treatment of 20 patients by this method, with recovery in 16 and notable improvement in 4, were cited

Use of this route in the presence of central-nervous-system involvement, in intraocular conditions, and some cardiac and renal disease would seem contraindicated

Acute brucellosis was treated by Criscuolo [151] by the intravenous injection of *Brucella* vaccine. In 9 cases he noted no good

results and in 4 patients there was intolerance. He discontinued its use. The author has confined the intravenous method of administration to the chronic illness.

An 83-year-old woman had suffered intensely for four months with neuritis, myositis, and arthritis involving the entire left arm The extremity was exquisitely tender, swollen from finger tips to shoulder, and was constantly cradled in a sling or pillow. There had been recurrent attacks of vomiting, diarrhea, headache, backache, malaise, neuralgic pain throughout the body, and low-grade fever of three years duration, which had yielded to intramuscular doses of *Brucella abortus* vaccine. They had produced unpleasant local and systemic reactions, with formation of cystic nodules, and had not favorably influenced the condition of the arm. She had had myocarditis, without decompensation, and a mild diabetes mellitus, for many years

A single intravenous dose of 250,000,000 heat-killed *Brucella abortus* organisms was followed by a sharp febrile reaction Swelling and pain disappeared by the fifth day and the function of the arm slowly returned to normal She remained relatively well, with occasional short courses of vaccine given intramuscularly, over a period of eight years. Desensitization had been brought about by the single intravenous dose of vaccine No reactions were noted following subsequent intramuscular doses She died at the age of 92, of senility. As pointed out, such severe reactions may be avoided by use of greater dilutions to initiate intravenous treatment, usually with equally as good clinical and phagocytic response.

Patients experiencing no systemic reaction to intravenous vaccine are as likely to develop phagocytic response as are those in whom definite reactions occur, furnishing further evidence of the specificity of *Brucella* vaccine as compared with foreign-protein shock therapy

Refractoriness to Brucella abortus *vaccine* (bacterin) has been noted in a large number of patients who had previously received mixed strains of *Brucella* organisms or culture filtrates with unsatisfactory effect In these patients desensitization has been more difficult and phagocytic response poorer, in notable contrast to the early and satisfactory clinical and serologic response to *Bru-*

cella abortus vaccine in patients not previously treated by these preparations. It is felt that several factors may have played a role in producing this refractoriness: (1) presence of *suis* and *melitensis* strains in the early treatment preparation, (2) use of larger dosage than was desirable, (3) use of too frequent dosage, (4) too prolonged use—all tending to induce lasting sensitization.

Results of Brucella Abortus *Vaccine Therapy*

Approximately 600 cases of chronic brucellosis have been treated with *Brucella abortus* vaccine (bacterin) and observed for periods of from one to fifteen years. It has been found that results of treatment cannot be tabulated as accurately as is desirable because of the impossibility of follow-up or classification by any wholly satisfactory means. Prior to the war, 247 patients, the great majority (96 per cent) in the chronic phase, were treated and most of them observed for periods ranging from one to nine years. It was thought that satisfactory results had been obtained in about 85 per cent of cases, with only partial recovery or no improvement in about 15 per cent. Of patients considered to have responded favorably, about 90 per cent had remained well for significantly long periods of time, with no recurrence of symptoms, the remainder had had one or more relapses, usually responding to additional short courses of vaccine.

Return to civilian practice after a lapse of several years allowed further observations among many of these patients, with a somewhat less favorable impression It was found that one 23-year-old patient had had recurrence of symptoms nine years after apparent recovery. Reinfection was possible but could not be proved In 15 patients vaccine therapy had been resumed after periods of from one to several years of good health, because of recurrence of symptoms, although reinfection from unpasteurized dairy products such as cheese or butter could not be ruled out In 11 other patients reinfection was a probability, all of them having had subsequent contact with infected cattle An occasional patient had had to resort to repeated courses of vaccine treatment in order to remain free of symptoms One patient had had recur-

rence of relatively severe illness referable to brucellosis, with various localizations, over a period of fourteen years, whenever vaccine was omitted for more than two months. She remained well and maintained a high phagocytic index for as long as vaccine was continued at seven- to fourteen-day intervals, and usually for a month or more after it was discontinued entirely.

Also difficult of assessment is the relative role played by vaccine treatment when it is used in conjunction with other methods, such as chemotherapy, antibiotics, fever therapy, or localized short-wave diathermy. In some instances it is notable that marked improvement but not recovery follows vaccine treatment but that lasting recovery follows combined therapy.

The factor of spontaneous recovery while under vaccine therapy may be a further cause of confusion in evaluating results. However, in patients who have been ill for from months to years, it should not be too difficult to distinguish rapid and satisfactory response to treatment from gradual, natural improvement, unless enthusiasm is allowed to becloud judgment.

Letters have not proved a satisfactory follow-up method Only those patients who remained well over a period of five or more years can be said to have recovered. Others who have had systemic or localized disease since vaccine treatment was discontinued cannot be classified because any of those conditions may have been due to *Brucella* infection or to unrelated etiology

The problem of assessment of results of treatment is less in the acute illness, but still is not wholly accurate, however long the period of observation It is manifestly impossible to state that any given method of treatment was responsible for freedom from recurrence since it is known that some untreated acute cases have but one single acute episode and then remain free of symptoms indefinitely An unknown factor, common to acute and chronic brucellosis, is the possibility of recurrence of *Brucella* infection under guises which are not recognized.

There may be other difficulties in evaluating results of treatment. A patient may state that he has not improved at all, that treatment has been a failure, that he feels as bad as ever. If one

fails to elicit the comparison with his previous state (ability to work, fatigability, fever, weight gain, joint manifestations, and the like) impression of failure may be had, whereas partial or complete recovery may have occurred. These patients may have an unconscious desire for escape through illness. Occasionally the converse is true, the patient being so anxious to attribute magic effect to his treatment that he claims recovery whereas definite failure is evident.

There is no definite laboratory criterion of recovery or cure, comparable in accuracy to the blood-complement-fixation test for syphilis, to supplement clinical judgment.

It is to be expected that a lower percentage of complete recoveries will be found in consultation practice because of the refractory nature of the cases which are referred, as compared with previously untreated patients

The present impression is that about 50 per cent of all adequately treated chronic cases have remained well, including those patients who had had symptoms for several years before vaccine treatment was initiated. (The chronicity of infection in previously untreated patients has seemed to play a surprisingly unimportant role in response or lack of response to vaccine treatment) Apparently 10 to 15 per cent of patients are properly classified as failures, for various reasons, including refractoriness to treatment, inadequate treatment. or other concurrent disease The remaining 35 to 40 per cent make up those patients who, although much improved, need further desensitization and or stimulation of antibodies through one or more additional courses of vaccine, from time to time.

Behind this reasoning lies the possibility that *Brucella* infection, once contracted, may be ineradicable If this is true it is a potential source of further manifestations but maintenance of a state of desensitization and relative immunity play most important roles in determining lasting recovery. Newer methods of treatment may alter the view as to permanence of infection.

Results of Treatment of Children

Brucellosis in childhood should be considered separately in evaluating results of vaccine therapy Childhood infection yields more rapidly and more lastingly than in older subjects, perhaps because infection is necessarily more recent, or because the organism is less likely to become entrenched in tissue or cells not altered by previous disease. Among 427 consecutive patients tabulated, 39 were children under 16, in the chronic phase of the illness Of these patients, all of whom received *Brucella abortus* vaccine, only 5 were refractory to treatment, requiring more than one course of vaccine. Of these 5 children, 1 had pulmonary localization and slowly recovered over a period of four months A second had a serious psychologic problem which interfered with treatment and probably with recovery The third child relapsed nine years later or was reinfected. The fourth had osteomyelitis of both femurs, not recognized as of *Brucella* origin until eleven years after the onset. In the fifth patient the diagnosis of brucellosis was questionable. In all the others apparently complete recovery occurred after short courses of vaccine (4 to 12 doses) and no symptoms referable to brucellosis have been known to recur over periods of from five to fifteen years It is safe to say that about 86 per cent of children responded promptly and completely to treatment and that the remaining 14 per cent responded slowly or less completely. There were no failures except in the patient in whom diagnosis of brucellosis remained in doubt

Hagebusch and Frei,[285] in their study of 182 children with brucellosis, also reported lack of enthusiasm for intravenous typhoid vaccine, dyes, and intravenous arsenicals A greater tendency to relapse was noted following Brucellin therapy than from *Brucella* vaccine used in subtolerance dosage Foshay's detoxified vaccine was effective in about 80 per cent of the chronic cases, about 50 per cent of these remained well after treatment was stopped. About 20 per cent had recurrence of symptoms but responded to further treatment and about 20 per cent failed to respond to any treatment.

Until such time as a drug, whether an antibiotic or a known chemical compound or other agent is available which will eradicate *Brucella* from tissue and tissue cells, *uniformly, in all patients,* regardless of chronicity or localization of infection, and with no lasting toxic effects, antigenic therapy will remain an invaluable method, especially in the chronic illness. Its value as an adjunct to antibiotic and other therapy has been discussed. It *is unlikely* that the *organism can* be *eradicated in* all patients, *from* all foci In these patients desensitization and immunization are essential. It *is* possible that *Brucella* allergy may persist following actual eradication of the organism; for these patients also desensitization may be necessary.

Chapter X

PROPHYLAXIS

> If all milk were efficiently pasteurized or boiled before being consumed, there would be no brucellosis excepting in those occupational groups whose work brings them into contact with infected animals or infected carcasses (*Public Health Reports,* July 15, 1938.)

BECAUSE of the infectiousness of dairy products other than milk (cheese, butter, buttermilk, ice cream) it is necessary to include these foods in the same category as milk and cream The milk and cream which goes into their manufacture also should be pasteurized, unless subjected to adequate heat in the process of manufacture. Aging of cheese does not appear to achieve absolute safety, even if it is greatly prolonged. Meyer[453] stated that there is only one way to make cheese safe and that is by pasteurization Evidence is quoted on pages 51–56 which makes this conclusion inescapable Authorities in the cheese industry have stated that all types of cheese may be made from pasteurized milk if the manufacturer so desires However, it must be admitted that the flavor of some pasteurized milk cheeses, however long aged, will not be as good

The major weakness in heat-treatment of milk and other dairy products as a prophylactic measure lies in its inability to protect those occupational groups where infection is developed by direct contact. Stockyard and slaughter-house employees, butchers, meat dealers, chefs, farmers, dairymen, ranchers, horse breeders,

Until such time as a drug, whether an antibiotic or a known chemical compound or other agent is available which will eradicate *Brucella* from tissue and tissue cells, uniformly, in all patients, regardless of chronicity or localization of infection, and with no lasting toxic effects, antigenic therapy will remain an invaluable method, especially in the chronic illness. Its value as an adjunct to antibiotic and other therapy has been discussed. It is unlikely that the organism can be eradicated in all patients, from all foci In these patients desensitization and immunization are essential. It is possible that *Brucella* allergy may persist following actual eradication of the organism; for these patients also desensitization may be necessary.

The difficulties in this program of eradication of the infection in animals are evident. Damon and Fagan [155] pointed to the urgency of measures to control animal brucellosis.

Since mother's milk must be considered as a potential source of infection to the infant (p 42), it seems inadvisable for the mother who has had a recent *Brucella* infection to nurse her child.

Pasteurization of Dairy Products

The efficacy of adequate pasteurization in reducing the incidence of brucellosis in human beings needs no discussion. When brucellosis occurs in persons living in regions where only pasteurized milk and milk products are sold there are other obvious explanations. Most apparent of these are: (1) ingestion of raw milk on trips to the country or other communities where raw milk is used, (2) infections acquired years before, remaining latent or subclinical until the clinical phase is precipitated by the debilitating effect of other illness, or until recognized by careful clinical and laboratory study, and (3) direct contact with infected animals or animal tissue The origin of infection, unless occurring in epidemic form, is often too obscure to allow accurate conclusions Since the incubation period can vary so greatly, since the infection can go unrecognized for so many years, and since the chronic illness so greatly predominates, epidemiologic methods are largely ineffective Only when brucellosis occurs in epidemic form can epidemiologic investigation be successfully applied It is fallacious to base statistics on the incidence of the acute illness or to try to incriminate any milk supply or other source of infection in isolated cases of infection, unless it is the only possible source of infection Such a situation in the adult would be rare indeed

For example, a 60-year-old woman spent a part of each summer for many years in a rural community where raw milk was used and where the herds were known to be infected. She presented laboratory and clinical evidence of brucellosis in 1934, apparently of four months duration Her home was in a large suburb of New York City where it was assumed that she had

cattle breeders, sheep, goat, and swine herders, and veterinarians, all of necessity may be in contact with virulent organisms if the disease in animals cannot be eradicated. These persons number over 10,000,000 * in the United States and, in some parts of the world make up the greater part of the population. The possible danger of handling uncooked meat in the home has not been evaluated.

The problem of eradication of the disease in domestic animals therefore must be considered as basic. If it can be accomplished, *pasteurization will cease to play the vital role that it now does* in protection of the general population against brucellosis. If eradication of animal infection fails, pasteurization must remain as the sole bulwark against mass infection, perhaps supplemented by immunization of those in whom exposure is unavoidable.

This third possible means of prophylaxis—immunization of individuals—is still uncertain, as to method and reliability. It will be discussed from the standpoint of present progress but with no conviction as to its practical application. Laboratory workers would constitute one group of unprotected persons even if eradication of infection in animals becomes a reality.

Lehr [432] expressed the opinion that brucellosis in man can be reduced if not eradicated, and that eradication of the infection *in animals will inevitably lead to the eradication of the disease* in man His recommendations were:

1 Compulsory testing of all swine, goats, and cattle
2 Branding and sale of all infected animals to packing houses having Government inspectors
3 Prohibition of sale of infected animals to individual butchers
4 Reimbursement of farmers for forced sale of infected animals
5 Compulsory calfhood vaccination
6 Education of meat-cutters and packing-house personnel as to safe measures for handling infected animals, such as the wearing of rubber gloves

* Dr James H Steele, Chief of the Veterinary Division, U S Public Health Service, estimates that 40,000,000 persons in the United States are potentially exposed by direct contact if all members of farm families are considered

The following is reproduced from *Health News*,[321] published by the New York State Department of Health:

THE SAFEST MILK IS PASTEURIZED

To those who by preference or conviction still buy the raw milk directly from the farmer, Walter D Tiedeman, Chief of the Department's Bureau of Milk Sanitation, has offered convincing proof that efficient pasteurization is the best known protection against milk-borne disease.

Prompted by recent evidence that there are a few who continue to advocate the use of raw milk, Mr. Tiedeman has issued a statement to the press in which he cites figures from the department records as the strongest argument for pasteurization In the 28 years from 1917 to 1944, he points out, there were 173 milk-borne outbreaks of communicable disease in upstate New York affecting 10,300 persons, 168 were traced to raw milk

In several of the 5 outbreaks attributed to pasteurized milk there was reasonable certainty that contamination following pasteurization by a bottling plant employee who had an undiscovered illness was responsible.

In another instance, unrecognized cases of disease on a farm apparently were responsible Furthermore, the efficiency of the pasteurizing plant had been in question previously, raising doubt as to whether the milk was actually pasteurized. In still another case, the milk was labeled "pasteurized" although the evidence indicated that it had not been pasteurized

Pasteurization as a means of assuring safety in milk supply cannot justly be discredited by the conditions mentioned, all of which are extreme exceptions to the rule and in marked minority.

Tiedeman was quoted as follows

"The most important reason for pasteurizing milk is that it provides the surest means of destroying disease bacteria By no means are all cases of communicable disease chargeable to milk Nevertheless, the occurrence of over 10,300 cases of milk-borne infection, not including tuberculosis and undulant fever, in 28 years, is no small matter. Undulant fever is a seriously disabling disease frequently due to the use of raw milk or cream from herds infected with contagious abortion. Increasing numbers of cases are being discovered in New York State,

always had pasteurized milk. Later it was found that she had been using raw milk in her suburban home and that infection was rampant in the dairy herds. No further attempt to locate the source of her infection was made. She was advised to avoid raw milk anywhere—that suburban *Brucella* were equally likely to produce infection as were rural *Brucella*.

Another patient considered that his chronic illness had been contracted in London where his business had kept him during the war and where unpasteurized milk had been used. The major manifestations of his illness had developed some months after he had taken up residence there. Inquiry brought out additional facts. He had had an undiagnosed recurrent chronic illness, which may or may not have been brucellosis, for several years prior to his use of raw milk in London. He had made business trips to various parts of the United States, Mexico, China, India, and South America, using milk, cream, and cheese freely, regardless of its status as to pasteurization.

Such cases are not the exception but are the rule, in a population that is so constantly on the move as are Americans.

In 1928 Carpenter and Boak [114] found that pasteurization for twenty minutes at 140° F. was sufficient to kill all *Brucella* organisms. Hardy and his coworkers [295] in 1930 stated that controlled pasteurization was effective against organisms of the *Brucella* group, finding no organisms in milk exposed to temperatures of 144 to 145° F for thirty minutes, followed by rapid cooling by refrigeration Organisms were cultured from one sample in which the temperature had fluctuated from 139 to 142° F However, Arnold [29] reported, in the same year, that living *Brucella* had been found after exposure to the temperature of commercial pasteurization In 1931 Boak and Carpenter [76] concluded that existing requirements for pasteurization (heating to 142 to 145° F for from twenty to thirty minutes) were adequate for destroying the most virulent strains of *Brucella*. Virtually all evidence produced by laboratory and epidemiologic investigation since that date has confirmed the fact that pasteurization is an effective method of killing *Brucella* organisms.

TABLE XII

AMERICAN CITIES WITH COMPULSORY PASTEURIZATION (INCOMPLETE) *

ARIZONA
- Phoenix

CALIFORNIA
- Coalinga
- Fresno
- Monterey County
- Pleasanton *
- San Francisco
- Sanger
- San Jose *
- Vallejo *

COLORADO
- Denver
- Palisade

CONNECTICUT
- New Haven

FLORIDA
- Fort Pierce
- Tampa

GEORGIA
- Savannah
- Waycross

ILLINOIS
- Aurora
- Calumet City
- Calumet Park
- Chicago *
- Chicago Heights
- Cicero *
- Elmwood Park
- Evanston *
- Homewood
- Joliet
- Kenilworth
- Lanark
- Morris
- Oak Park *
- Olno
- Ottawa
- Peru *
- River Forest *
- Riverside *
- St Charles

ILLINOIS (continued)
- Wilmette *
- Winnetka
- Woodstock

INDIANA
- Anderson
- Bremen
- East Chicago
- Elkhart
- Fort Wayne
- Gary
- Goshen
- Greenfield
- Hammond
- Hope
- Indianapolis
- Logansport
- Mishawaka
- Nappanee
- Richmond
- Shelbyville
- South Bend
- Terre Haute
- Valparaiso
- Warsaw
- Whiting

IOWA
- Sioux City
- Traer

KENTUCKY
- Harrodsburg *

LOUISIANA
- New Orleans *

MARYLAND
- Brunswick
- Frederick

MASSACHUSETTS
- Ayer *
- Boston
- Brookline *
- Cambridge *
- Everett *
- Milton *

MASSACHUSETTS (continued)
- Somerville *
- Watertown *
- Wellesley *
- Winchester *

MICHIGAN
- Detroit
- Durand
- Highland Park *
- Melvindale *
- St Joseph *
- Wyandotte

MINNESOTA
- Winona

MISSOURI
- St Louis *

MONTANA
- Libby

NEVADA
- Reno

NEW JERSEY
- Dumont
- East Newark
- Hackensack *
- Hoboken *
- Keyport
- Newark *
- Teaneck
- Trenton *
- Union City *

NEW YORK
- Auburn *
- Batavia
- Buffalo
- Clifton Springs
- Cortland
- Elmira *
- Freeport *
- Geneva *
- Hudson Falls

most of which are believed to have been contracted through the use of raw milk or cream from infected cattle."

The J.A.M.A. commented editorially as follows on pasteurization (133:249, 1947):

PASTEURIZATION OF MILK

The value of pasteurization of milk in preventing the spread of milk-borne disease is now well established The Council of Foods and Nutrition of the American Medical Association in an official statement says, in part. "The pasteurization of milk is a public health measure. The public should demand pasteurized milk for drinking and the use of pasteurized milk in milk products. The dairy trade should universally adopt pasteurization in the interest of public health Only pasteurized milk is granted recognition by the Council There is no cogent evidence that pasteurized milk is significantly inferior nutritionally to raw milk" Progressive city health departments have long required compulsory pasteurization, in 1943 the Boston Health Department succeeded in adopting a regulation putting an end to the sale of raw milk in that city . . .

In spite of all evidence to the contrary there are still many persons who believe, or profess to believe, that raw milk is more nutritious, richer in essential vitamins, and of better taste. The majority of dissenters stress the flavor The factual story of a freight agent at a small railway station furnishes an enlightening commentary. He had received a shipment of pasteurizing equipment consigned to a local dairyman About a month thereafter he notified the dairyman that he would have to discontinue buying his milk because he did not like its flavor since it was pasteurized. The dairyman invited the agent to come to his farm where he showed him the pasteurizing equipment still in its crates Hartsock[314] quoted a dairyman who encountered such popular aversion to pasteurized milk that he pasteurized the milk without labeling it as such, there was not a single complaint about the taste of the milk

Although the data appearing in Table XII indicate the wide-

by the question as to whether the malted milk was to be made with pasteurized milk. The answer was in the negative. When asked if other drug stores or restaurants in the city served pasteurized milk, he was emphatic in stating that they did not.

During a visit to Mexico in 1946, the author was repeatedly assured that the milk, cream, and dairy products served were pasteurized. A government-licensed guide confirmed this statement, adding that in all probability, the products were not goat's milk but rather cow's milk—but definitely pasteurized. On inquiry from a scientific authority in that country, it was learned that they were largely goat's milk and its products and that none was pasteurized. If doubt as to milk exists a simple expedient is to ask that it be scalded. A dilemma was solved in a restaurant in a resort community of Georgia several years ago in the following fashion: The waiter was asked if the cream served with coffee was pasteurized. He did not recognize the word "pasteurized." He was then asked if the cream was raw. That term too was not familiar to him—but ultimately he produced the desired information. It was canned.

Brown[85] stated: "It appears to me that in attempts to reduce the incidence of human brucellosis we are confronted by a public health dilemma. Pasteurization of raw milk might reduce the incidence of human brucellosis 50 per cent; on the other hand, it might reduce the number of immunized persons in the population to such an extent that there would be an increased incidence of clinical brucellosis, especially in those occupations and regions where exposure to cutaneous infection with *Brucella suis* is a major factor. I admit that successful elimination of brucellosis from dairy herds would have the same effect. As a means of avoiding the exposure to infective doses of *Brucella*, I have more confidence in raw milk from a herd of cows under strict brucellosis control than in commercially pasteurized milk from cows that are not under such control. There are many slips in commercial pasteurization technique. I know of an unpublished experiment in

TABLE XII (*continued*)

AMERICAN CITIES WITH COMPULSORY PASTEURIZATION (INCOMPLETE) *

NEW YORK (*continued*)
- Kingston [a]
- Lake Placid [a]
- Liberty
- Mt Vernon [a]
- New Rochelle [a]
- New York
- Niagara Falls
- Poughkeepsie [a]
- Rochester [a]
- Saranac Lake
- Tonawanda [a]
- Walton

NORTH CAROLINA
- Tarboro

NORTH DAKOTA
- Bismarck
- Dickinson
- Mandan

OHIO
- Barberton
- Bellevue
- Cleveland Heights [a]
- Cincinnati
- Dayton
- Girard
- Hamilton
- Lakemore
- Lockland [a]
- Lorain
- Massillon
- Oakwood
- St. Bernard
- Sidney
- Toledo [a]
- Warren
- Wellington

PENNSYLVANIA
- Easton [a]
- Pittsburgh

RHODE ISLAND
- Newport [a]

SOUTH CAROLINA
- Charleston

TEXAS
- Corpus Christi
- El Paso

VIRGINIA
- Norfolk [a]

WASHINGTON
- Grandview

WISCONSIN
- Cudahy
- Lake Mills
- Milwaukee [a]
- Racine [a]
- Sheboygan
- West Milwaukee
- Whitefish Bay

* Source Sanitary Engineering Division, Milk and Food Section, Federal Security Agency, United States Public Health Service (September, 1945).

This list is incomplete. H. A. Harding estimates that more than 250 municipalities in the United States now require the pasteurization of all milk or of all but Certified Milk (Bulletin of the Mathews Co, Detroit, July 11, 1945). Many additional cities without compulsory pasteurization nevertheless have 100 per cent of their milk supply pasteurized

[a] Cities requiring pasteurization of all market milk except Certified (51) All others listed require all market milk to be pasteurized (103).

spread use of pasteurized milk, it is still common to find communities in the United States where raw milk is the only form available. In the summer of 1939 it was found that a modern-looking drug store in Bennington, Vermont, served only raw milk and ice cream made from raw milk at the fountain The proprietor proudly proclaimed that pasteurized milk was not likely to be found in *that* state [a] In the autumn of 1946 a similar experience with the exclusive sale of raw milk was encountered in Montgomery, Alabama. The drug store proprietor was annoyed

[a] In recent years Vermont has taken active steps to encourage pasteurization

ized. He stressed the fact that 62 outbreaks of milk-borne disease had occurred in the United States between 1925 and 1943 attributed to pasteurized milk, as contrasted with only 1 outbreak attributed to Certified Milk (raw). Not mentioned was the fact that the relatively small amount of Certified Milk sold also could account for the rarity of the outbreaks. It is probable that Rolls Royces kill fewer pedestrians than do Chevrolets.

Relatively large outbreaks of milk-borne disease are the only ones that are likely to come to the attention of the public health authorities. The scattered distribution of Certified Milk may help to account for its low rate of incrimination in sporadic *Brucella* infections. More often than otherwise the onset of brucellosis is so insidious as to preclude accurate epidemiologic appraisal of date or means of exposure, particularly because more than one possible source of exposure is likely to exist

The statistics of Tiedeman (p. 493) also tend to lessen the force of Brown's statements as to the relative frequency of milk-borne outbreaks from raw and pasteurized milk. Brown listed 712 outbreaks of disease attributed to raw milk as compared with 62 outbreaks of disease from pasteurized milk (a ratio of 11 5 to 1) in the United States between 1925 and 1943. Tiedeman reported 168 milk-borne outbreaks attributed to raw milk as compared with 5 outbreaks from pasteurized milk (a ratio of 33 6 to 1), in upper New York State between 1917 and 1944 New York State had a much higher percentage of pasteurization than the nation at large. Tiedeman was able to explain the outbreaks attributed to pasteurized milk on the basis of contamination following pasteurization in "several instances," inefficiency of the pasteurizing plant and unrecognized illness on a farm in another instance, and failure to pasteurize in still another It is possible that similar causes could have been found for the 62 outbreaks cited by Brown

Excellent arguments in favor of Certified Milk made by Brown included the following (1) hogs are not allowed to mingle with cows in these herds, (2) frequent testing of milk whey for *Brucella*

which guinea pigs fed commercially pasteurized milk contracted brucellosis. *A maximum of safety from exposure to milk-borne* Brucella *would be obtained by the exclusive use of pasteurized milk from a herd under strict brucellosis control.*" (Italics are the author's.) There can be no disagreement with the statement that "a maximum safety from exposure to milk-borne *Brucella* would be obtained by the exclusive use of pasteurized milk from a herd under strict brucellosis control." "Strict brucellosis control" alone cannot exclude *Brucella* infection. Pasteurization of Certified Milk comes as near to the ideal as is possible under existing conditions.

The thesis advanced by Brown is not an adequate argument against pasteurization. Even if there were epidemiologic evidence that real immunity is acquired through acquisition of subclinical *Brucella* infection with the less virulent *abortus* species, it would seem to be a heroic means of protection against the more virulent *suis* infection, particularly because only a small segment of the population is forced to expose itself to direct contact with *Brucella suis*. It would seem sensible to give a maximum degree of protection to 90 per cent of the population through pasteurization of dairy products and to continue to develop methods for protection of the other 10 per cent.

That the label "pasteurization" in itself is not a guarantee against milk-borne infection is admitted. Raw milk may be sold under such a label if the dairyman chooses to compromise with his conscience and risk detection Inadequate pasteurization cannot be expected to kill *Brucella* or other pathogens. However, the phosphatase and other tests for adequacy of pasteurization, combined with competent inspection of milk handlers, of dairies (including cattle), and of pasteurizing plants, and the automatically recorded records of the operation of the plant, reduce deliberate or accidental noncompliance to a minimum

Brown [84] stated that the public health record of Certified Milk * is unsurpassed by that of any other grade of milk, raw or pasteur-

* The name is copyrighted with the use of capital letters and apparently should be so used

	Certified Milk	*Grade A Milk*
VETERINARY SUPERVISION		
Veterinary inspection of farm and cows	Monthly	Annually
Tuberculin tests	Semiannually	Annually or as required
Brucella tests	Agglutination tests of blood required. Retest within 3 months if no reactors	No testing usually required
ADMISSION TO HERD	All cows admitted or readmitted after freshening must be approved by veterinarian	No veterinary examination usually required.
TIME OF DELIVERY	48 hours after day produced.	48 hours after day pasteurized. No time limit from production until pasteurized.

In agreement with Brown, it is felt that the dosage and dilution factors in *Brucella* infection are important in preventing a high incidence of human brucellosis from raw milk Cream is known to be a more potent source of infection than whole or skimmed milk. Outbreaks involving large milk supplies are likely to cause a lower morbidity rate than when the milk from one infected cow is used by a family (p 87) (This furnishes an excellent reason for home pasteurization under such circumstances) The role of dilution in any herd, except one in which a large percentage of the cows are infected, allows ingestion of fewer bacteria It is likely that a smaller percentage of infected cows would be present in

agglutinins (not required in other grades of milk), (3) more frequent blood-agglutination tests than in production of other grades, thereby *reducing* the likelihood of retention of infected cattle (although not eliminating it), (4) greater cleanliness of stables, milking operation, and milk handling than is demanded in other herds, (5) more frequent inspections by designated inspectors than are required in other herds.

There can be no disagreement with the viewpoint of Brown that Certified Milk—pasteurized—furnishes "a double safe-guard enjoyed by no other grade of milk."

CERTIFIED RAW OR GRADE A RAW

Some of the requirements that apply to Certified Milk as compared to those usually applied to Grade A milk were listed by Wilson [711] as follows:

	Certified Milk	*Grade A Milk*
MAXIMUM BACTERIA, STANDARD PLATE COUNT		
Raw	10,000 per cc.	100,000 to 200,000 per cc.
Pasteurized	500 per cc.	30,000 per cc.
MEDICAL SUPERVISION OF EMPLOYEES	Medical examination and special tests of employees repeated annually. Families of employees under medical supervision. Weekly medical inspection by physician	Farm employees must not have or carry communicable disease, but no examination or medical inspections usually required. Employees in milk plants usually required to have a medical certificate.

misleading. It is *still* generally recognized that the vast majority of brucellosis in human beings is attributable to infected milk or other dairy products, except in those occupational groups who come in direct contact with infected animals. In countries such as Mexico, where most milk is boiled, cheese made from raw milk has been reported as the greatest source of infection (pp. 55, 82).

An article in the September, 1947, issue of *Hygeia* unintentionally gave the impression that the hog is a greater menace to human health than the cow, and that pasteurization was of lesser importance than commonly considered. Rice[570] stated: "There is substantial evidence to indicate that as much as 70 per cent of the human infections observed are of swine origin, caused by *Brucella suis*" The *New York Herald Tribune* on September 28, 1947, headed a news item: "Undulant Fever Laid Mainly to Pigs, Not Cattle" Dr. Rice responded to a letter asking if it was his intention to say that *Brucella suis* was responsible for that much *Brucella* infection throughout the United States, promptly disclaiming such intent Rather, he intended that his comment apply to the hog-raising regions of the United States and not to the country as a whole.

STATISTICS ON PASTEURIZATION

It is difficult to present accurate figures as to the actual percentage of raw milk sold in the nation at large. Lists compiled by the U. S Public Health Service were incomplete, as of September, 1945 (Table XII). It was known that in 31 states 103 cities required pasteurization of all market milk and that 51 cities required pasteurization of all market milk *except Certified* It was estimated by H A Harding (*Bulletin* of the Mathews Co, Detroit, July 11, 1945) that more than 250 municipalities in the United States required pasteurization "of all milk *or of all but Certified*" (Italics are the author's, and are intended to stress the regrettable fact that often no distinction in statistics is made between Certified raw and pasteurized milk.) It was further pointed out by the U S Public Health Service (Sanitary Engineering Division),[243] that information compiled up to March 20,

a herd producing Certified Milk than in other herds less carefully supervised.

Brown stated that the public has been bombarded with sensational articles in popular magazines and that the impression was given by one article[307] that anyone drinking a glass of raw milk is in imminent danger of contracting undulant fever. As stated elsewhere, the sensationalism of some popular magazines is to be deplored, particularly in the field of human health and disease. In the instance referred to, it was the unauthorized and reprehensible editorial changes that were responsible for the sensational nature of the article. Whereas the objectionable editorial changes included the hypothetical outbreak in "Crossroads, U.S.A.," the fact is that fatalities have occurred in various parts of the world as the result of milk-borne outbreaks of brucellosis (p. 86). There was a mortality of 21.4 per cent in an outbreak of 14 cases in Connecticut, reported by Horning.[242] Mazza[483] quoted mortality rates as high as 35 per cent in one province of Argentina. In general any truthful article in the press or magazines that arouses the public to the menace of raw milk serves a valuable purpose. This article, objectionable though it was because of unauthorized and unjustifiable editorial changes, did not give the impression mentioned by Brown that "if all milk were pasteurized there would be no human brucellosis." It stated that, "The disease spreads in other ways [other than through raw milk] —persons who handle cows, pigs, goats and other animals may contract it. But milk is the worst hazard." The implication was obvious—that milk is the worst hazard to those who do not come in direct contact with infected animals.

That infected milk is not the sole cause of human brucellosis is well recognized (p. 38). That this can be used as a reason for failure of pasteurization is absurd. The cited observations of Hardy[25-] that "the incidence of recognized brucellosis in man tends to vary directly with the extent of the hog raising industry" whereas "it was previously assumed, as a result of the studies of the Mediterranean Fever Commission that brucellosis was acquired through the ingestion of infected raw dairy products" seem

total percentage of pasteurized milk, from 93 per cent in 1942 to 96.3 per cent in 1945. However, more than 10 per cent of the milk sold in six counties of New York State still was raw milk in 1945. In one county 19.1 per cent was raw milk. Whereas in most counties there was a decrease in raw milk used from 1944 to 1945, in nine counties there was an increase. Educational efforts, made largely by the New York State Department of Health, and the effect of sanitary regulations, have been successful in the main. However there can be no relaxation in the campaign for a goal of 100 per cent pasteurization.

HOME PASTEURIZATION

Simpson[630] described a method of home pasteurization: The milk is placed in an aluminum vessel and heated to 155° F. (68.3° C.) while it is stirred constantly. The vessel is then immediately set in cold water and the stirring continued until the milk is cool.

The following is quoted from the bulletin entitled *Home Pasteurization of Milk and Cream* issued by the New York State Department of Health in 1946:

DIRECTIONS FOR HOME PASTEURIZATION OF 4 QUARTS OR LESS OF MILK IN A DOUBLE BOILER

Materials

Raw milk
Double boiler
Heat (cook-stove burner)
Thermometer reading to 170° F. or higher
Spoon or stirrer
Clean, scalded container for pasteurized milk
Cold water or ice and water
Cold storage space (refrigerator)

Method

1. Place cold or warm water in the bottom section of the double boiler.

1946, indicated that "at least 389 municipalities located in all sections of the country required pasteurization of all milk *or of all except Certified.*" On the state level it seems evident that no state requires that all milk sold within the state be pasteurized.

Fuchs[215] estimated that in municipalities of over 1,000 population the percentage of raw milk had risen from 74.7 per cent in 1936 to about 80 per cent in 1945; in cities of more than 10,000 population he estimated that the increase had been from 83.1 per cent to near 88 per cent in that same period.

In November, 1944, the U. S. Public Health Service, Sanitary Engineering Division, Milk and Food Section, published a *List of American Communities in which the Milk Ordinance Recommended by the Public Health Service is in Effect*, consisting of 8½ typed pages. Excerpts are quoted as follows: "Inclusion in the list means that the State Health Department has reported that the milk ordinance in effect in that community is the Public Health Service Milk Ordinance without downward revisions, or changes in grade names, or significant changes in the form of the ordinance. . . . Inclusion in the list does not necessarily imply that the ordinance is being satisfactorily enforced. Lack of proper enforcement does not, therefore, bar from inclusion. . . . The percentage of market milk which is pasteurized is indicated immediately following the names of the communities for which this information has been reported. *High-grade pasteurized milk is safer than high-grade raw milk because of the added protection of pasteurization*" (Italics are the author's.) This list is available on request from the U. S Public Health Service.

It should be borne in mind that communities listed as having less than 100 per cent of pasteurized milk may have changed that status for the better since the data were compiled. Claims of partial or complete pasteurization of milk supply apparently do not guarantee satisfactory enforcement of the milk ordinances. Further inquiry in any locality is recommended.

Relatively little raw milk is sold and consumed in New York State. Even during the war years there was a gradual increase in

total percentage of pasteurized milk, from 93 per cent in 1942 to 96.3 per cent in 1945. However, more than 10 per cent of the milk sold in six counties of New York State still was raw milk in 1945. In one county 19.1 per cent was raw milk. Whereas in most counties there was a decrease in raw milk used from 1944 to 1945, in nine counties there was an increase. Educational efforts, made largely by the New York State Department of Health, and the effect of sanitary regulations, have been successful in the main. However there can be no relaxation in the campaign for a goal of 100 per cent pasteurization.

HOME PASTEURIZATION

Simpson[616] described a method of home pasteurization: The milk is placed in an aluminum vessel and heated to 155° F. (68.3° C.) while it is stirred constantly. The vessel is then immediately set in cold water and the stirring continued until the milk is cool.

The following is quoted from the bulletin entitled *Home Pasteurization of Milk and Cream* issued by the New York State Department of Health in 1946.

DIRECTIONS FOR HOME PASTEURIZATION OF 4 QUARTS OR LESS OF MILK IN A DOUBLE BOILER

Materials

Raw milk
Double boiler
Heat (cook-stove burner)
Thermometer reading to 170° F. or higher
Spoon or stirrer
Clean, scalded container for pasteurized milk
Cold water or ice and water
Cold storage space (refrigerator)

Method

1. Place cold or warm water in the bottom section of the double boiler.

2. Place raw milk in the top section of the double boiler and set the top into the bottom section and place over the burner Do not apply heat directly to the milk.
3. Place a clean thermometer in the milk and stir gently with a clean spoon. Watch the thermometer and heat the milk as quickly as possible to at least 160° F., stirring continuously.
4. As soon as the thermometer reads 160° F. remove the top section of the double boiler and dump the hot water.
5. Fill the emptied lower section of the double boiler or preferably a larger pan with cold water or ice and water and cool the milk as rapidly as possible to 50° F. If no ice is used, it is necessary to change the water several times Rapid cooling improves the flavor.
6. Pour the cold milk into a covered container which has been cleaned and scalded. Under no circumstances must a raw milk container be used for pasteurized milk unless after being washed it has been completely immersed in boiling water for at least one minute If desired, the milk can be cooled to about 100° F., then bottled and cooled further in the bottle, but the slower cooling may impair the flavor of the milk.

DIRECTIONS FOR HOME PASTEURIZATION OF ABOUT 10 QUARTS OF MILK

Materials

Raw milk
Milk pail—preferably a 10-quart seamless steel pail, well tinned and provided with a tight fitting cover
Water pail—sufficiently large to contain the milk pail, and high enough to permit the water to be at a slightly higher level than the milk in the inner pail
Pie tin—perforated bottom
Thermometer—preferably a mercury-in-glass, reading to 170° F. or higher, and graduated to 1° F scale division
Spoon or stirrer
Heat—large cook-stove burner
Cold water—preferably running cold water
Cold storage space—refrigerator or ice water cabinet

Method

1. Place the perforated pie tin in an inverted position in the bottom of the water pail
2. Fill the 10-quart pail with milk and place it on the pie tin in the larger pail
3. Add cold or warm water to the outer pail to a height slightly above the level of milk in the inner pail
4. Place the pail within a pail over the burner.
5. Stir the milk continuously with the spoon, especially after it reaches a temperature of 140° F.
6. Continue heating until the milk reaches 158° F. (The slightly lower temperatures for larger quantities of milk is made possible by slower rates of heating and cooling)
7. Cool immediately to as low a temperature as possible by placing the milk container in cold water or by running cold water into the outer pail
8. Place the cover on the milk pail and store in ice water or in a refrigerator at a temperature below 50° F.
9. If the milk pail is too large to store conveniently, transfer the milk to smaller clean, scalded containers.

This bulletin, prepared by the Division of Sanitation, is obtainable by residents of the State of New York from the New York State Department of Health, Albany, New York, on request. The bulletin points out the fact that milk so treated cannot legally be labeled "pasteurized" and offered for sale

Two of the large mail-order companies have marketed different types of electric home pasteurizing apparatus

The prospectus of one states that the cost of pasteurization is approximately 2½ cents for each 2 gallons of milk The apparatus consists of an outer compartment which is filled with 2½ gallons of water, 2 gallons of milk are then placed in the tinned milk kettle suspended within the unit The agitator is started and the timer control is set The milk is automatically heated to 143° F and kept there for 30 minutes, by means of a thermostat It operates from 110–120 volt alternating current

The other apparatus has the following features. It is made of alumi-

2. Place raw milk in the top section of the double boiler and set the top into the bottom section and place over the burner. Do not apply heat directly to the milk.
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Cold storage space—refrigerator or ice water cabinet

remained negative in dilutions of 1:25 on numerous tests, before and after isolation of the organism. One other cow had a high blood-agglutination titer at a previous test, subsequently became negative and remained so but continued to shed the organisms in the milk. Another cow which had never showed a blood-agglutination titer beyond 1:50 showed agglutinins and organisms in the milk. Organisms in the udder and agglutinins in the milk were occasionally found in the absence of agglutinins in the blood.

The lowering of the blood-agglutination titer in the previously reacting cow is commonly accepted as evidence of improvement or cure in that animal. In the presence of a low titer, following a diagnostically significant titer, such cows may be returned to milking herds from which raw milk is sold. The findings of Meyer and Huddleson bear out the author's contention that a lowering blood-agglutination titer or a negative reaction following a reaction in high titer cannot be accepted as evidence of freedom from *Brucella* infection. It is difficult to understand why such criteria ever were used.

Inadequacy of the Whey Agglutination Reaction

Various workers have stated that agglutination reactions performed on milk serves as an additional safeguard. Way [695] felt that the rapid agglutination test done on milk as a check on the blood-agglutination reaction would allow "reasonably safe" use of raw milk, if both were negative. Fitch and Bishop [219] found agglutination reactions of 1:100 in 2 samples of whey of milk from a herd producing Certified Milk. Guinea-pig inoculation revealed *Brucella abortus*. They recommended use of agglutination tests on milk whey of herds as one means of detection of infection. If titers even as low as 1:5 were found in herds not recently blood tested, more careful investigation of those herds would be indicated. They felt that the method would not detect all infected herds but, if applied routinely, would be effective in detecting milk samples coming from badly infected herds.

num of 1-gallon capacity and is intended to pasteurize milk for an average family three or four times a week. Because of the heat distribution jacket and milk container, which are constructed "to create agitation by convection," no water bath, agitator, or gear system is used Quick cooling is accomplished by lifting the milk container from the machine and placing it under an open faucet. It operates from 110-120 volt alternating current. A buzzer sounds when pasteurization is completed.

Inadequacy of Blood Testing of Cattle

It has long been the contention of the author[210] *that negative blood-agglutination reactions in cattle, as in human beings, does not insure the absence of* Brucella *infection.* Borts[71] stated in 1945:

Attempts to control brucellosis in cattle and hogs by the blood agglutination test have been only fairly successful. The chief difficulty with the blood testing program and the removal of reactors has been that highly infectious animals in the incubating stage of the disease are sometimes left in the herds, when blood titers are either negative, or 1:10 or 1:20 A test of these animals at a later date may show them to be reactors in high titer, indicating that at the first test the animals were in the early stages of the disease. It has been further observed that cattle and hogs may remain chronically infected and a source of infection with the blood agglutination titers negative or below that considered as suspicious or positive. A comparable situation is seen in man, the blood cultures frequently being positive many days to weeks before agglutinins are established in the blood in diagnostic titers.

Infection in milk from nonreacting cattle has been demonstrated repeatedly In 1936 Doyle and Beckett[181] reported isolation of *Brucella abortus* from the milk of 2 cows in which the blood-agglutination tests had been negative. They reported similar experiences of various others prior to 1936 (p 45).

Meyer and Huddleson[479] in 1938 reported isolation of *Brucella abortus* from the milk of 3 cows in which blood agglutination

remained negative in dilutions of 1:25 on numerous tests, before and after isolation of the organism. One other cow had a high blood-agglutination titer at a previous test, subsequently became negative and remained so but continued to shed the organisms in the milk. Another cow which had never showed a blood-agglutination titer beyond 1:50 showed agglutinins and organisms in the milk. Organisms in the udder and agglutinins in the milk were occasionally found in the absence of agglutinins in the blood.

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However, Meyer and Huddleson[479] reported on the relationship between blood and milk agglutinins as follows: Among 705 cows showing blood-agglutination reactions in a titer of 1:200 or higher, 273 or 38.7 per cent showed no agglutinins in their milk. The milk from 88 (32.3 per cent) of the 273 cows yielded *Brucella* on culture. It was not unusual to find cows with negative agglutination reactions in the milk in which *Brucella* was found on culture. The organism was found to be present in the udder for long periods of time without showing agglutinins in the milk. *In the majority of animals studied* Brucella abortus *appeared in the milk before agglutinins appeared in the milk.* They concluded that oftentimes there is little if any correlation between the presence of *Brucella* in the milk and the presence of agglutinins in the milk.

It can safely be concluded that, like the blood-agglutination reaction, in animals and man, the milk-agglutination reaction is valuable if positive but of no proved significance if negative.

In the presence of such findings as these, it is apparent that occasional or even frequent blood testing of herds, with negative results, or with removal of reactors, does not make a raw milk supply entirely safe. If agglutination tests on milk are used as an added precaution it can only reduce the number of cattle which are giving milk-borne infections to man, and which are infectious to other cattle

Early Detection of Infection in Animals

An attempt was made to determine what other means of investigation might lead to earlier and more reliable diagnostic tests than the blood-agglutination reaction alone in domestic animals Little recent work has been carried out with the allergic skin test Crawford[148] quoted the findings of Live and his coworkers, in agreement with those of earlier investigators, the main disadvantage of allergic agents was the tendency to stimulate the production of agglutinins in brucellosis-free cattle, thus interfering for a considerable period with any subsequent blood-agglutination testing and to induce positive skin reactions in a signifi-

cant number of animals where no other evidence of brucellosis could be demonstrated. Meyer and Hardenbergh[486] had reported on the unreliability of the skin test in cattle in 1913.

Work done at the Agricultural Research Administration of the Bureau of Animal Industry in Beltsville, Maryland, on the opsonocytophagic reaction of cattle indicated that a definite and fairly persistent index may be expected in animals which are infected, vaccinated, or otherwise exposed to the antigenic effect of *Brucella* organisms Opsonins were also transferred to the young in the colostrum Crawford[145] stated, however, that they were unable to demonstrate any practical value of the test, either as an indication of infection or as a measure of resistance.

Because of the recognized limitations of the blood-agglutination test for diagnosing swine brucellosis, considerable effort has been made recently to develop an efficient skin test, Crawford stated Preliminary results with different types of experimental *Brucella* extracts indicated that test agents so far employed are hypersensitive Although a few *Brucella* infected animals may be identified that would otherwise be missed on the blood-serum–agglutination test, they also elicited skin reactions in some noninfected animals (Such animals may have inapparent infection) In general, the agreement between the blood-serum–agglutination and intracutaneous test was approximately 75 per cent.

Since swine may be infected with virulent strains of *Brucella suis* for years without production of agglutinins,[355] diagnosis of the disease and its eradication may be even more difficult than in cows The farmer whose swine are allowed to come into proximity with his cattle risks infection of the cattle and then of human beings with the virulent *suis* species

Huddleson, Wood, Kressman, and Bennett[368] described the bactericidal and growth-inhibiting action of bovine blood plasma for *Brucella abortus* in which sufficient differences were found in the action of plasma from infected and noninfected cows to differentiate one from the other, regardless of the agglutination titers This may prove to be of practical importance in earlier

detection of infected animals in which agglutinins are present either in low titer or entirely absent.

Further studies are urgently needed, including reevaluation of the blood-complement-fixation reaction.

Control Methods in Cattle

Miller, Wight, and Crawford[190] summarized the evidence in favor of various control plans in cattle. They stated:

> At the end of the seventh year of test and slaughter it was estimated that the incidence of Bang's disease had been reduced about 50 per cent through the removal of over 2 million reactors. The slaughter of Bang's disease reactors was initially developed as a part of a cattle reduction program. From a strictly disease control point of view, however, and this latter viewpoint must now be accepted as our aim, test and slaughter was not entirely without just criticism. It did not lend itself well to the beef-type herds under range conditions; the so-called "problem herds" slowed up the program; breaks in clean herds, varying from 2 to 5 per cent, were disturbing We must accept the fact, however, that test and slaughter is still one of our most useful and practical methods of control. Its use is necessary in dairy herds, the milk from which must, by municipal regulation, be from cows negative to the blood test The test and slaughter method is indicated also, in sections in which the incidence of Bang's disease is very low, as in many of the southern states and in the "area plan" when conditions are favorable. And we must not lose sight of the fact that test and slaughter must be the final operation in those herds in which reacting animals are held until vaccinated replacements become available, and undoubtedly in most of those herds in which adult vaccination is practised.

The failure of the test and slaughter method to eradicate infection in cattle was suggested by the report of Winter of the New York State Department of Agriculture. He stated in *Veterinary Medicine* (July, 1947), that of all the herds in New York State under this plan that were free from evidence of infection on

January 1, 1944, more than one-half revealed reinfection in the succeeding fifteen months.

Miller and his coworkers [490] stated that the policy of the Bureau of Animal Industry of the United States Department of Agriculture was to approve the application of three separate methods of control:

> test and slaughter,
> test and slaughter, with calfhood vaccination;
> test and retention of reactors, with calfhood vaccination.

They considered the second plan (test and slaughter with calfhood vaccination) to be acceptable. A herd resistant to infection could be developed in a few years by the continued vaccination of calves, using strain 19 They recommended the addition of calfhood vaccination in herds in which test and slaughter is being practiced, especially in herds in which accreditation is being delayed by spread of infection, and in localities where there is a relatively high incidence of infection.

Of the test and retention of reactors with calfhood vaccination, the authors stated that·

> The admission of negative replacements in herds being freed of this disease has long been recognized as a procedure accompanied by danger. In some instances the residual herd consisting of the more resistant animals would remain free from infection while the replacements for removed reactors would contract brucellosis and abort, thus continuing the disease To provide satisfactory control measures in such herds, plan C, or test and retention of reactors, with calfhood vaccination, was approved This permits the retention of productive reactors until vaccinated replacements become available A valuable factor that has developed in this connection is that some reactors lose their positive blood status in two, three or four years and may be retained permanently in the herd [In the author's opinion, retention of a previously reacting cow in which subsequent tests are negative is based on the false assumption that a negative reaction indicates cure of that animal's infection (p 508)]

The present need for increased production has been a factor for the

detection of infected animals in which agglutinins are present either in low titer or entirely absent.

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Miller concluded that calfhood vaccination is a more orderly procedure than adult vaccination in negative herds and that if there is no urgency for the vaccination of adults, their resistance may be established in a few years by calfhood vaccination.

It seemed apparent from their experience that the use of adult vaccination in a control program is limited to those herds in which other methods of control do not appear to be applicable Their specific recommendation for whole herd vaccination was as follows: In incipient infection; in beef herds in which calf production is the chief herd requirement, it is done when cows are open or in early pregnancy, in so-called problem herds; and in large, infected dairy herds in which calves are not raised and in which there is a rapid turn-over of animals as a result of milk production demands. In the last-mentioned type of herd they recommended that all replacements should also be vaccinated In all herds in which whole herd vaccination is practiced, calfhood vaccination should be continued, they felt. The best age for vaccination of calves was said to be about 6 months.*

Calfhood vaccination using strain 19 was considered by Haring and Traum [296] to have passed the experimental stage as early as 1941 This attenuated strain, carefully supervised by the U. S. Bureau of Animal Industry, has been kept virulent enough to produce immunity but not enough to produce infection. They pointed out that it has been possible to build negative herds from badly infected ones within a few years by the use of this vaccine when replacements are limited to vaccinated heifers reared on the same farm.

In spite of the efforts being made, Huddleson [355] stated in October, 1946, that *Brucella* infection in cattle is now more extensive than ever before He felt that the vaccination program has not served to eradicate the disease, that many animals lose their immunity within a year, many others within two years, and most of them within three years. After prophylactic vaccination

* These data are published through the courtesy of B T Simms, Chief of the Bureau of Animal Industry, Agricultural Research Administration, U S Department of Agriculture

increased demand for this type of control. Difficulty in obtaining replacements and their high cost are contributing factors In some states, notably New York and Vermont, control measures are based on this plan almost exclusively.

VACCINATION OF CATTLE

Miller stated that research done by the Bureau of Animal Industry indicates that vaccination is as effective in adult cows as in calves. The principal reason that adult vaccination of cattle is not advocated under all conditions is that the vaccinal agglutination titer tends to persist for indefinite periods in adult cattle whereas in calves it tends to disappear within three to twelve months after vaccination. They pointed out that this persistence of titer interferes with the control program which is based on the agglutination test.

Use of strain 19 in vaccination of adult cattle in advanced stages of pregnancy may result in abortion. In one instance a herd of approximately 60 negative cows was vaccinated because of infection in a neighbor's cows which had wandered into the premises. These animals were from five to six months pregnant; 23 aborted within one and a half to three months after vaccination The culture from one of these aborting animals was sent to the Bureau of Animal Industry laboratory where the strain was found to be of an organism of reduced virulence not positively identifiable as strain 19. There was clinical evidence that the abortions were due to the injections of the strain 19 vaccine.

In another instance, in a herd of 46 beef-type animals, in which brucellosis was present and in which abortion had been occurring for several years, adult vaccination was practiced when the animals were from five to six months pregnant During the next three months 2 abortions occurred. A culture recovered from the fetus of one of these proved to be similar in most respects to strain 19.

They pointed to another factor in adult vaccination in dairy cows—there occurs an immediate loss or drop in milk production which persists from one to two weeks after vaccination.

He came down with brucellosis in about 16 days. When heifers first come in milk we consider the raw milk to be just as dangerous when infection results from vaccination as if it had been acquired in the natural course of events."

Milk and cream produced under such circumstances demands pasteurization even more urgently than from herds presumably uninfected but unvaccinated (p. 37).

CHEMOTHERAPY OF BOVINE INFECTION

Schuhardt,[613] stating his belief that the sulfonamdies ordinarily fail to penetrate the mammary glands of the infected cow, thus accounting for relapse, produced experimental evidence that sulfanilamide and sulfapyridine alone, of all of the sulfonamides, came through the mammary glands in good concentration Of the two sulfapyridine seemed the better. The amount needed may render it economically prohibitive, however The method does not furnish the answer to the problem of eradication of infection in domestic animals in general, even if it proves practical and successful in individual animals or herds Reinfection would be very likely to occur It is unlikely that chemotherapy will play a large role in the control of animal infection.

PROPHYLAXIS IN SWINE

A unit-segregation system of eradicating swine brucellosis, under conditions existing in California, was described by Cameron.[105] He considered that the method might prove much more difficult or even impractical in states where a great deal of swine breeding was carried on The basis of the unit-segregation system largely consisted of the breaking of the chain of infection from infected sows to bred-gilt, and from aborting gilt back to the resistant but potential spreader sow.

It is apparent that the problem of control of infection in cattle and other domestic animals has not yet been solved Whatever the method used it would seem necessary that it be applied on a

of cattle it becomes impossible to determine which animals are infected and which are reactors due to vaccine.

In 1943 Huddleson[352] suggested the possibility that active immunity to *Brucella* infection may be produced by using a fraction of live *Brucella* organisms. Using a Booth and Green bacterial crushing mill to obtain from live *Brucella abortus* and *Brucella suis* a highly complex soluble fraction, he found that an important degree of protection was conferred upon guinea pigs. The duration of immunity seemed to be about six months. He felt that it is not necessary to inject live *Brucella* organisms or for the organisms to multiply within the body of the host in order to produce an active immunity against brucellosis and that any agent which will raise the resistance of highly susceptible guinea pigs to a sufficient degree to protect them against virulent *Brucella* organisms will likewise, when used in suitable doses, stimulate sufficient immunity to protect humans and large animals against infection from natural exposure.

In 1946 Huddleson[353, 355] stated that mucoid and mucoid daughter-phase cells produced inhibiting antibodies in high titer when injected into guinea pigs, rabbits, or cattle and that active immunity against *Brucella* infection with that species of *Brucella* was engendered in guinea pigs. These mucoid strains were said to produce no infection in themselves, in contrast with the infectiousness of strain 19. Further, it was said that agglutinins are unlikely to be produced by this method, or, if produced, that they will occur only in titers of 1:25 or 1:50, persisting for only about sixty days, in contrast with production of agglutinins in high titers by use of strain 19.

It is apparent that no method devised to date is either uniformly effective or without important drawbacks.

INFECTIOUSNESS OF STRAIN 19

Tiedeman[605] stated that there was "some recent evidence that the attenuant vaccination would cause brucellosis in humans. The report is that a student injecting some of the vaccine in some manner let the syringe slip and got some of the vaccine in his eye.

absence of abortions, infected cows were found to produce about 20 per cent less milk.

Basing his figures on an estimate of 10 per cent of infection in Michigan cows (which total about 1,080,000), Huddleson considered that the 108,000 infected cows produced about 2,063 pounds less milk per animal per year, or a total milk loss of 222,804,000 pounds of market milk yearly, enough to supply about 557,000 persons for one year. The loss in butter was about 11,140,200 pounds per year, or enough to supply 655,300 persons for a year He further estimated that there is a loss of about 16,240 calves per year in Michigan, because of abortion or sterility due to *Brucella* infection, representing a loss of 1,299,200 pounds of veal, or 6,494,000 pounds of beef per year, if dairy cattle are sold for beef, or a proportionate loss in dairy products if the calves were to be raised as milk-producing animals.

Similarly convincing and startling figures were quoted to show the loss in pork products from infection in swine. Since no accurate estimate of the incidence of the disease among swine has been compiled, Huddleson quoted the observations made on one large hog-raising farm where 119 gilts and sows were bred to farrow in the spring of 1944 Blood tests were positive in 53 (44 per cent). The expected pig crop was 371 but only 70 pigs were raised, a loss of 82 per cent or 54,180 pounds of dressed pork. Then, as the result of efforts to eradicate the disease that same farmer's loss from 194 gilts and sows bred the next year was reduced to 17,820 pounds

These figures, multiplied by the proper factor to represent all the milk, butter, veal, beef, and pork not produced in the United States would, as Huddleson pointed out, seem fantastic. There is no doubt of their approximate correctness. In themselves they furnish adequate reason for continuing all efforts at eradication of the infection in animals, as well as in man

nationwide or even a hemispheric basis to render it effective. It serves but a temporary and partial purpose to confine efforts to single or scattered areas and then to allow reinfection to occur through sale or exchange of animals from other areas. If infection in an entire state could be eradicated, embargo against importation of animals from other states could be only partly effective since state boundaries cannot serve as barriers to farm-to-farm spread of infection. On the other hand, if complete immunization of cattle proves successful and if it can then be extended to hogs, sheep, goats, and horses, a practical solution will have been achieved, in spite of continued presence of infection in wildlife.

Economic Factors

Economic factors are best viewed from the standpoint of animal infection alone since fairly accurate statistics in cows, goats, and hogs are available for some states of the union, and since animal loss can be directly translated into food loss and money loss. Human infection unquestionably also entails a tremendous economic loss in workdays, productivity, and the cost of being ill, but cannot be evaluated accurately for obvious reasons. (Lee and Jones [429] estimated that the cost of each human case of brucellosis, in lost time, medical care, and laboratory services, amounted to $325.) The actual number of persons ill with brucellosis in a country or its subdivisions cannot be determined with any degree of accuracy if the chronic illness is included.

Huddleson,[354] stating that brucellosis is one of the major causes of food losses, discussed milk yields in *Brucella*-infected cows compared with those not infected. The data were based on the pooled results of various investigations The annual milk yields of 542 noninfected animals were compared with those of 389 considered to be infected. The average infected animal produced 2,063 pounds less milk per lactation period than those not infected, with the smallest difference 660 pounds and the largest 3,832 pounds, the average decrease was 23 per cent. Even in the

absence of abortions, infected cows were found to produce 20 per cent less milk.

Basing his figures on an estimate of 10 per cent of infec Michigan cows (which total about 1,080,000), Huddleson c ered that the 108,000 infected cows produced about 2,063 p less milk per animal per year, or a total milk loss of 222,8 pounds of market milk yearly, enough to supply about 5 persons for one year. The loss in butter was about 11,1 pounds per year, or enough to supply 655,300 persons for a He further estimated that there is a loss of about 16,240 per year in Michigan, because of abortion or sterility d *Brucella* infection, representing a loss of 1,299,200 pounds o or 6,494,000 pounds of beef per year, if dairy cattle are sc beef, or a proportionate loss in dairy products if the calves to be raised as milk-producing animals

Similarly convincing and startling figures were quoted to the loss in pork products from infection in swine Since no rate estimate of the incidence of the disease among swin been compiled, Huddleson quoted the observations made o large hog-raising farm where 119 gilts and sows were br farrow in the spring of 1944 Blood tests were positive in per cent). The expected pig crop was 371 but only 70 pigs raised, a loss of 82 per cent or 54,180 pounds of dressed Then, as the result of efforts to eradicate the disease that farmer's loss from 194 gilts and sows bred the next yea reduced to 17,820 pounds

These figures, multiplied by the proper factor to represe the milk, butter, veal, beef, and pork not produced in the U States would, as Huddleson pointed out, seem fantastic. Th no doubt of their approximate correctness In themselves furnish adequate reason for continuing all efforts at eradic of the infection in animals, as well as in man

Prophylactic Vaccination in Man

Many attempts have been made to immunize human beings with *Brucella* vaccines since the first reports by Wright[728] in 1897.

Meyer and Eddie[481] reviewed the attempts made to induce immunity by *Brucella* vaccine from 1908 to 1941. Infection occurred in some workers supposedly immune. They quoted the opinion of Taylor, Lisbonne, and Vidal (1938) as follows: "Our attempts to protect animals by killed vaccine and the occurrence of 7 cases of undulant fever among the personnel associated with this investigation, all of whom had received prophylactic vaccination, leave us with little faith in protecting man in this manner." They also quoted their own work and that of Huddleson in the attempt to immunize monkeys to *melitensis* strains by inoculating them with live *abortus* strains. When their resistance was subsequently tested by cutaneous injection of dilute suspensions of a recently isolated *melitensis* strain, febrile reactions resulted and *Brucella melitensis* was isolated from 3 of the 5 monkeys. Their conclusions were that antigen injections fail to prevent laboratory infection

The danger to laboratory workers of all categories, including those not only employed in the building but in contact with animals, their pens, the dust, laboratory glassware, and the like, led Meyer and Eddie[481] to make various recommendations for their protection They advised that no experiments involving *Brucella melitensis* be assigned to nonimmune workers, because of its greater virulence Until beginners or students could be implicitly trusted as to technic or until they had developed agglutinins or a phagocytic index above 5 * and a skin allergy, they were assigned to projects involving contact only with *Brucella abortus* material They considered some to be immune by inheritance and some through having had subclinical infections. They

* An index above 50 would furnish more reliable evidence of resistance to infection (p 316)

advocated careful and constant vigilance and the judicious use of rubber gloves. This regimen led to cessation of new infections among their laboratory workers.

An attempt to immunize laboratory personnel against laboratory infection was made by Howe and his coworkers,[315] using "a *Brucella* vaccine." Among an unstated number of vaccinated persons, 17 developed acute relapsing illness lasting from about four months to more than two years, with an average of six months. It could not be stated whether the attempt to immunize was a complete failure or whether the course of the illness was somewhat altered.

Prophylaxis in veterinarians is extremely difficult, especially in those doing obstetric work in cattle. Wearing of arm-length rubber gloves is one of the few measures that may be effective.

Kolmer, Bondi, and Rule[409, 410] reported more encouraging results in attempts to immunize human beings. They used a mixed heat-killed vaccine containing 1 billion organisms each of *B. typhosus*, *Br. abortus*, and *Br. melitensis* per cc. Three doses of 0.5 cc., 1.0 cc., and 1.0 cc. respectively were given subcutaneously at seven-day intervals to 29 adults. Mouse protection tests before vaccination showed no survivals of mice which were given the serum from 24 of the 29 human subjects. Agglutinin and phagocytic response were considered significant. Mouse protection tests against the *abortus* strain after inoculation showed that the serum of 23 subjects showed some protection, corresponding to an increase of about 62 per cent. None of the sera before vaccination showed complete protection before immunization, whereas 8 (28 per cent) showed complete protection after immunization. Protection against the *melitensis* strain occurred at a somewhat higher level.

One year later, Kolmer[409] reported the following observations on the 25 subjects who were followed.

a. 22 sera were positive for protective antibody against *Brucella abortus*,

b. 25 sera were positive for protective antibody against *Brucella melitensis*.

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vaccine in a small series of presumably noninfected persons usually met with only temporary phagocytic response of moderate degree By contrast, patients actively infected, regardless of whether or not they had had previous successful stimulation of phagocytic response by means of *Brucella* vaccine, are likely to respond to intradermal or intramuscular killed *Brucella* organisms with rapid and often sustained increase in phagocytic activity.

From incidental as well as purposeful observations and from the observations of others the impression is gained that immunization of uninfected persons by the use of *Brucella abortus* vaccine, intradermally, intramuscularly, or intravenously, is unlikely to be successful in a large proportion of persons It must again be stressed that there are no absolute criteria to determine absence of past infection or presence of subclinical current infection in selecting groups of persons for experimental study.

Laws Concerning Pasteurization of Dairy Products

There is a wide variation in laws governing the sale of milk and cream and its products in various cities and states throughout America No purpose would be served in compiling data from all New York City requires pasteurization of all milk and cream except Certified Milk. This also applies to buttermilk, and to ice cream and other frozen desserts Cheese sold in the city of New York must be pasteurized, or aged for at least 60 days after manufacture at a temperature not lower than 35° *There is no specific regulation requiring the pasteurization of butter.* Whereas most of the large commercial firms selling butter in the city of New York pasteurize the cream from which the butter is made, some butter made from raw milk is sold.

In the State of New York, exclusive of New York City, laws allow the sale of Certified pasteurized, Grade A pasteurized, Certified (raw), Special A raw, and Grade A raw. The New York State Sanitary Code requires that any form of raw milk be produced from cattle "which have passed the tuberculin test, and are free from Bang abortion disease, and are free from mastitis,

At the end of two and a half years, the results in 20 subjects followed (5 were not available) were:

a. 3 sera were positive for protective antibody against *Brucella abortus.*
b. 18 sera were positive for protective antibody against *Brucella melitensis.*

This attempt at active immunization against *Brucella* infection seems to have been successful, so far as could be proved by laboratory methods. The loss of mouse protection in 3 sera of 25 at the end of one year, and in 17 of 20 at the end of two and a half years suggests the need for reinoculation—perhaps at yearly intervals—in order to maintain the measurable immune response, if this method of immunization proves feasible.

Carpenter [113] stated that prophylaxis vaccination in man has not been carried out on large scale, but that observation in a small number of persons continually exposed to the *Brucella* indicates that protection may be afforded by this procedure. He advised the use of the standard *Brucella* vaccine injected intramuscularly in amounts of 0.1, 0 2, and 0.3 cc. at weekly intervals, adding that further studies on the prophylactic vaccination are essential to establish its value.

Foshay [239, 240] stated his belief that it would require a tremendous amount of antigen in normal individuals or animals to induce immunity. He knew of no reliable criterion of degree of protection obtainable by prophylactic vaccination other than demonstrated by exposure to infection He suggested that the infection rate in vaccinated veterinary students be studied after they had been in practice for five years, ten years, and longer, or that vaccination of half of each graduating class be carried out and that they be observed for ten years In two small-scale attempts at *Brucella* prophylaxis results were very poor, men who had extraordinarily high phagocytic power became infected within three months from exposure to risky laboratory work.

Attempts by the author to induce measurable immunity (phagocytic response) following intradermal use of *Brucella abortus*

sale of butter made from unpasteurized cream. It seems probable that the sale of all raw milk and unpasteurized dairy products ultimately will be illegal.

Medicolegal Aspects

A precedent has been established for holding dairymen and distributors responsible for the production and sale of milk from infected cattle On April 26, 1937, Superior Judge James T Lawler of Seattle, Washington, ruled that milk distributors and producers are liable for the purity of their products. Ralph Dean was awarded $1,946 50 for having contracted brucellosis, in a suit against the company distributing the milk and the farmer who produced it. The London *Times,* on March 18, 1939, reported the award of £195 in damages to Harry Harmer against I. Cornford, a dairyman, in a similar suit. The justice of such awards is open to question unless it could be proved beyond reasonable doubt that infection could be traced to the suspected milk supply. Except in the presence of epidemics, such proof rarely can be adduced since previous infection may have occurred with a long period of latency However, the dealer, or hotel or restaurant operator, who sells raw milk must be prepared to prove that the milk could not be reasonably suspected of infectiousness when epidemiologic data tend to incriminate it Uniform laws concerning liability of dairymen and purveyors in general are needed, for the protection of the producers as well as of the public.

In 1932 a butcher in New York State was awarded compensation for *Brucella* infection complicated by endocarditis, arising out of his occupation In 1933 undulant fever was held compensable under the Workmen's Compensation Act of the State of Idaho Meyer and his coworkers [485] called attention to the fact that the California State Industrial Accident Commission had declared undulant fever contracted in the slaughter-house and in the laboratory as compensable. Del Sel [173] quoted the case of a butcher who claimed that he contracted brucellosis in the employ of the Municipal Slaughter House of Buenos Aires, Argen-

and are subjected to physical examination by a licensed veterinarian at intervals of not more than 3 months (in the case of Special A raw). Grade A may be produced from 'milking animals' free from Bang abortion disease" The State of New York has regulations similar to that of New York City regarding the sale of cheese made from unpasteurized milk. Apparently it is the ultimate aim of the State of New York to bring about pasteurization of all milk, gradually, by education rather than by compulsion.

CHEESE

In New York State it has been illegal since November 15, 1944, for any wholesaler, assembler, or broker to release any cheese—including that made from stirred or washed curd—to the retail trade unless it is pasteurized, made from pasteurized milk products, or aged in accordance with regulations. Unless the cheese itself is subjected to heat treatment equivalent to pasteurization, as in processing, it is required to be made either from milk, skim milk, or cream which has been pasteurized, or the cheese is required to be ripened or cured at a temperature of not less than 35° F. for a period of not less than sixty days from the date of manufacture All cheese in wholesale trade is required to be labeled with the name and address of the manufacturer or an [illegible] or symbol printed on each quarter [illegible] urized," if the cheese is pasteurized, [illegible] date of manufacture.

In the State of Colorado a holding period of one hundred and twenty days for cheese made from raw milk is required by law.

Concerning foreign cheeses, Riggs[574] stated "To the best of my knowledge the pasteurization of milk for cheesemaking of Limburger, Muenster, Camembert, Brie, Edam, Gouda and Swiss is not generally practiced On the other hand, Cheddar cheese made in New Zealand and Australia is very largely from raw milk. I understand however that Canada has a 90 day holding period requirement for Cheddar cheese."

There seems to be an obvious need for regulations governing the importation of cheese and for tightening of regulations as to

industrial surgeon) recognized more promptly that the process was due to brucellosis.

As in all other disease, the aim in *Brucella* infection is prevention rather than treatment, no matter how successful the latter may be. At present it cannot be said truthfully that eradication of *Brucella* infection from man and animals is in immediate view. However, by continuing the efforts which are steadily gaining momentum in both prophylaxis and therapy, it is felt that this infection will be relegated to the status of typhoid fever, to become all but a medical curiosity among civilized people.

tina. He was awarded compensation for a period of sixteen months. The fact that this award was made on the erroneous assumption that persons contract brucellosis "almost only upon contact with animals infected with it" is an interesting but irrelevant commentary, for the facts of the case pointed to the patient's occupation as the actual source of his infection.

Laboratory infection is compensable under the workmen's compensation laws in various states A young female laboratory worker employed in North Carolina was awarded compensation because of *Brucella* infection presumably contracted from direct contact with organisms in 1940.

Harding [289] quoted *Health News* (California) of June 20, 1938, as having reported the discontinuance of an application for injunction and a suit for damages of $100,000 against Dr. George Parrish, Health Officer of Los Angeles, because of his distribution of a circular pointing out the dangers of raw milk.

There is still a disposition on the part of some industries involved in the handling, slaughtering, and sale of cattle and swine to oppose legal recognition of brucellosis as an industrial disease. In fairness to employees uniform laws are needed since there is no longer a question as to the infectiousness of infected animals and their fresh tissues to those who are in direct contact with them. In some instances such laws would react to the benefit of the industry as well At least there would be greater stimulus for research in the prevention of animal infection which presumably would lead to lessened incidence of contact infection.

Borts [71] called attention to reluctance of the packing industry to consider brucellosis as an occupational disease. He stated: "That brucellosis is an occupational hazard is not denied by those who are fully informed and are willing to admit facts and potentialities as they exist"

In the patient with periarthritis and low-grade osteomyelitis of the carpus described elsewhere (p 216), a sizable compensation award would have been obviated and the hand restored to a greater degree of usefulness a year earlier had the author (or the

industrial surgeon) recognized more promptly that the process was due to brucellosis.

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Chapter XI

ADDENDA

IN November, 1948, the Second Inter-American Congress on Brucellosis was held in Argentina under the auspices of the Pan American Sanitary Bureau. The valuable contributions made by the delegates from Mexico and Central and South American countries cannot be included here because of the unavailability of complete translations from the Spanish and Portuguese. The Third Congress is planned for Washington, D. C., in the Autumn of 1950. Other data of more or less importance has had to be omitted for various reasons.

Among other concepts concerning the prevention and treatment of chronic *Brucella* infection in man and animals that have not been adequately evaluated is the use of mineral "trace elements" for the replenishment of exhausted soil and for supplemental animal and human feeding. As yet nothing conclusive concerning it can be gleaned from the available literature

Additional observation in several patients with hypothyroid states in the presence of chronic brucellosis have borne out occasional previous findings Low basal metabolic rates with high blood cholesterol levels in the presence of mild to moderate symptoms of hypothyroidism have reverted to normal levels, along with reversal of the clinical syndrome, following successful treatment of brucellosis, the apparent etiologic factor

Much research, the results of which it had been hoped could be included in this monograph, has had to be deferred for lack of research funds. For example, it was felt by the author many

years ago that various diseases of unknown etiology should be investigated from the standpoint of possible relationship to *Brucella* infection and/or allergy. Among these diseases were arthritis, Parkinson's syndrome, and multiple sclerosis. It was not thought that brucellosis would be proved to be the sole cause of any of these diseases or syndromes but that it might be a contributory etiologic factor in some cases, as suggested by observations already made.

The relationship between brucellosis and a small percentage of all cases of arthritis had already been demonstrated (p 201) It was felt that larger groups of arthritics should be studied from the standpoint of *Brucella* infection, using complete diagnostic studies, and that, in those in whom there was sufficient clinical and laboratory evidence of coexisting brucellosis, a therapeutic trial of specific methods should be employed Only by such means could the actual facts be demonstrated.

As the result of the striking improvement in one case of typical Parkinson's syndrome (p 244) investigation of other cases was planned, on the theory that *Brucella* infection (or allergic reaction to it) may be one of possibly many etiologic factors.

No proof of any relationship between *Brucella* infection and multiple sclerosis exists Their coexistence in several patients may have been by pure chance It was realized that it would be difficult to demonstrate any possible relationship because of the tendency of multiple sclerosis to partial or complete spontaneous remission

Among the patients with multiple sclerosis treatment of the coexisting brucellosis was undertaken in only three In the first of these patients there were remissions following *Brucella* vaccine treatment which could not be distinguished from the natural course of the disease since this patient had had many previous remissions In the second patient there had been no remission prior to the use of aureomycin in November, 1948, fifteen months following the onset of neurologic disease Low-grade fever subsided during the short course of aureomycin and did not recur until two weeks after it had been stopped. Two months later

there was lessening of the hyperactive knee jerks, improvement in gait and diminution in the Babinski reflexes, along with better control of the bowel and increased energy. Additional treatment is to be given and observation continued.

A third patient with multiple sclerosis of two years duration and coexisting chronic brucellosis is under treatment with chloromycetin. Because this patient's neurologic manifestations had been steadily more marked before treatment, with no spontaneous remissions, it may be possible to evaluate the effects of chloromycetin therapy, if any are noted, more accurately than in patients whose histories indicate such spontaneous remissions.

Kyger and Haden (Brucellosis and multiple sclerosis: Cutaneous reactions to *Brucella* antigens. *Am. J M. Sc.* 216.689, 1948) have published observations on the possible relationship between *Brucella* infection (or allergy) and multiple sclerosis. They reported having reviewed the histories of 560 cases of chronic brucellosis, finding that sensory and motor changes or disturbances had been noted in 28 patients; in 2 additional patients the fully developed picture of multiple sclerosis had been noted. They then skin tested 118 consecutive cases of multiple sclerosis with *Brucella* antigen, finding 97 per cent of positive reactions to killed *Brucella* organisms, as compared with 21 per cent of positive reactions in a group of 56 rural residents having a variety of clinical disorders other than multiple sclerosis or encephalomyelitis, and 31 per cent of positive reactors in another group with neurologic disorders not in these categories Further evidence of active *Brucella* infection was found in the blood agglutination reactions with *Brucella* These were carried out in only a small number of the patients, unfortunately, 18 were negative and 5 positive in titers ranging from 1–20 to 1–320. However, the higher titers (1–160 and 1–320) were found in two patients who had already had skin tests, rendering the blood agglutination reactions questionable Rabbits and guinea pigs were inoculated with blood and spinal fluid of 5 cases of recently active multiple sclerosis A number of animals died of a granulomatous disease but cultures were sterile or contaminated, allow-

ing no conclusions They quoted the theory of Andren as to the role of local allergy in the vasoconstriction and occlusion in multiple sclerosis and observed that perivascular infiltration and small vessel thromboses have been noted as basic components of the granulomatous lesions produced by brucellosis. Their observations were summarized as follows. "The known pathologic features and geographic distribution of multiple sclerosis and brucellosis are not incompatible with some relationship."

It seems clear that further investigation, employing all of the known laboratory procedures for the diagnosis of brucellosis, should be carried out in a large series of cases of multiple sclerosis. These procedures should include cultures of blood and spinal fluid, using the special technic essential for the isolation of *Brucella*, animal inoculation, blood and spinal fluid agglutination reactions, opsonocytophagic reaction, blood complement fixation reaction, and, lastly, skin test with a dependable *Brucella* antigen. Cultural and histologic study of fresh autopsy material also possibly would be available. When brucellosis is demonstrated in any case of multiple sclerosis, a cautious trial of treatment of the *Brucella* infection or allergy should be undertaken. Such methods should consist of the use of an effective *Brucella* antigen in subtolerance doses, or of aureomycin or chloromycetin Dihydrostreptomycin or streptomycin, if used at all, would require great caution because of possible neurotoxic effect Prolonged observation of such patients will be essential to proper evaluation

Antibiotic Therapy. Additional Observations

Aureomycin *

Aureomycin is a yellow, crystalline antibiotic isolated from the substrate of *Streptomyces aureofaciens*. It is a weakly basic com-

* Acknowledgment is made to Lederle Laboratories for supplies of aureomycin and to Dr Stanton M Hardy, Medical Director, for helpful suggestions and cooperation in its use

pound containing both nitrogen and nonionic chlorine. It is available as the hydrochloride.

Treatment with aureomycin orally of 110 patients, all but one presumably suffering from chronic brucellosis, allowed observation as to the side-effects and tentative observations and conclusions as to its clinical effect. Previous reports have dealt solely with its use in acute infections of the virulent *melitensis* species (Spink, Braude, Castañeda, and Goytia: Aureomycin therapy in human brucellosis. *J.A M.A.* 138:1145, 1948) or with acute exacerbations of chronic brucellosis (Schoenbach, Bryer, and Long: The pharmacology and clinical trial of aureomycin: A preliminary report. *Ann N.Y Acad. Sciences* 51:267, 1948). There is ample evidence that the acute illness can usually be terminated. Recovery from the acute illness furnishes no criterion as to actual cure since it may only be the septicemic phase of the infection which is influenced These patients will have to be followed for long periods of time to be sure that the chronic phase does not follow the acute illness or that the acute episode will not recur.*

Among the author's patients treated with aureomycin was only one, in a subacute phase, in whom blood culture was positive. This 35-year-old man had been progressively more ill for a month before he was referred by Dr Irving Kramer in October, 1948, with a diagnosis of probable brucellosis. His complaints were extreme fatigue, malaise, nausea, diarrhea, sweats and chills, with daily fever ranging as high as 102 6 Blood agglutination reaction with *Brucella* had occurred in a titer of 1 160 and blood culture had been negative Physical examination was essentially negative Further laboratory studies showed a total white blood count of 5,550, with 48 per cent polymorphonuclear neutrophiles, 43 per cent lymphocytes, and 9 per cent monocytes, and a sedimentation rate of 76 mm /1 hour (Westergren) Blood culture was repeated using the Castañeda technic with the appearance of colonies at the end of four days These were subsequently identified as *Brucella* of the *abortus* species by Miss Anne Blevins of the New

* Harris, H J Aureomycin and chloromycetin in brucellosis *Bull N Y Acad Med.* 25 458, 1949

York Postgraduate Hospital Laboratory and by the Division of Laboratories & Research of the New York State Department of Health. The organism was determined to be susceptible to aureomycin in concentration of 0 78 microgram per ml. or greater.

For a year before the onset of the present illness he had noted fatigue, slight nausea, and anorexia each afternoon with no explanation for the symptoms despite adequate physical and laboratory examinations. He had had raw milk in childhood and again in 1945 while on a trip to Denmark

Aureomycin was given orally in dosage of 1 0 Gm every six hours for four days and then 0.5 Gm. every six hours for three days. Chills ceased within twenty-four hours, along with subjective improvement. Temperature fell to within normal range on the third day. Five days after the short course of aureomycin he stated that he felt well except for weakness and fatigue. However, sedimentation rate was still high (85 mm./1 hour, Westergren). White blood count was 5,100, with 36 per cent polymorphonuclears, 1 per cent basophiles, 55 per cent lymphocytes, and 5 per cent monocytes

Blood culture was repeated on November 2 and colonies of *Brucella* were noted on the ninth day In the meantime moderate sweating, fatigue, and mental confusion occurred Aureomycin was resumed on November 12, this time concurrently with sulfadiazine, both orally, and was continued for six days and then stopped because of vomiting apparently attributable to the sulfadiazine He again felt well except for one short episode of mild symptoms attended by fleeting temperature elevation to about 100° F On December 13 white blood count was 4,000, still with relative lymphocytosis, and a sedimentation rate of 39 mm /1 hour (Westergren) Temperature was 100° F A third blood culture initiated on this date resulted in the appearance of *Brucella* colonies on the sixteenth day It seemed probable that the organism had been attenuated by aureomycin or that fewer organisms were circulating in the blood. A third course of aureomycin was given, beginning on December 29, 1948, this time in gradually ascending doses, up to 2 Gm daily. A Herxheimer-like reaction

occurred two days later, with chill and fever to 102.2° F. and there was some difficulty in concentration and some fatigue and sweating. Treatment was interrupted for six days and then resumed with a subsequent lot of aureomycin which had been productive of lesser side-effects following additional processes of purification. On January 25, four days after concluding the third course of aureomycin, he reported feeling entirely well, having been free of sweats, fever, and other previous manifestations of brucellosis. White blood count was 4,700, with 60 per cent polymorphonuclears, 4 per cent eosinophiles, 34 per cent lymphocytes, and 2 per cent monocytes; sedimentation rate was 35 mm./1 hour (Westergren). Blood culture initiated on that date showed no growth in three weeks. On March 26, 1949, the patient seemed well. White blood count was 6,700 with 58 per cent polymorphonuclears, 2 per cent eosinophiles, 36 per cent lymphocytes, and 4 per cent monocytes, sedimentation rate was 25 mm./1 hour (Westergren) It is not sure that actual cure has been accomplished. The patient is still under observation.

All of the 109 chronic cases of brucellosis treated were selected for one of the following reasons. (1) The desirability of the eradication of the organism if such were possible, (2) The desire to avoid the known possible toxic effects of streptomycin; (3) The ease and economy of oral administration to the ambulatory patient as compared with hospital care for the administration of streptomycin parenterally, (4) The apparent freedom of aureomycin from any important degree of toxicity as suggested by its use in spotted fever, typhus, scrub typhus, and other infections, (5) The apparent ability of aureomycin to permeate the cell membrane, giving ground for hope that intracellular as well as extracellular *Brucella* would be susceptible to it.

Most patients had had previous treatment by various methods, with only partial or temporary recovery

The activity of *Brucella* infection was questionable in 16 patients There were 31 males and 79 females.

Dosage was initiated with 3 to 4 Gm. daily in the early phases

and later with 2 Gm. daily, halving the dose after 3 or 4 days, totalling 14 to 25 Gm., if tolerated. In children dosage was proportionately lower.

Side effects of rather marked severity occurred in 48 of the 79 females (60.7 per cent) and in 6 of the 31 males (19.3 per cent); 34 did not complete the course of treatment because of the severity of reaction. Symptoms consisted of headache, nausea, diarrhea, epigastric pain, and involvement of the mucous membranes

due to oral use of penicillin and closely resembling riboflavin deficiency, vaginal and anal itching and irritation occurred in 12, with slight vaginal and/or anal bleeding in five. Anal fissuring occurred in 3 patients. Not all symptoms occurred in all patients. Frequency of urination and bladder discomfort occurred in 3, with shedding of many epithelial cells in the urine. Generalized desquamation of the superficial layers of the epidermis in slight degree was noted in 3 patients.*

In most of the patients there was marked amelioration of symptoms as soon as the dose was halved and relief from symptoms within a day or two after cessation of treatment. In a few patients diarrhea, vaginal and anal irritation continued for several weeks following cessation of treatment.

Fever, probably attributable to aureomycin, occurred in 3 patients but was low-grade and of short duration.

Although several hundreds of patients suffering from a variety of other diseases, notably typhus, scrub typhus, and spotted fever, had previously been treated with aureomycin, most of them with larger doses than was employed by the author, reports of side-effects have only mentioned Herxheimer-like reactions and mild gastro-intestinal symptoms. O'Leary and his coworkers (*Proc. Staff Meetings, Mayo Clinic* 23:574, 1948) described vomiting and

* *Dermatitis* of severe degree developed within 2 days after initiation of treatment in 1 patient, and more slowly and of lesser severity in 3 others, following exposure to sunlight. There was abnormal uterine bleeding in 2 patients and subungual in 1.

"mild perlèche and smooth tongue indicating beginning vitamin B deficiency" in one patient. The severity of the illnesses may have masked the symptoms in some instances.

Because of severity of side-effects experienced early, dosage was further modified so as to determine the patients' tolerance before full dosage was employed and before marked symptoms could develop. This seemed to be justified by evidence that organisms susceptible to aureomycin apparently do not build up tolerance to it. Treatment of these patients was begun with 0.25 Gm. every eight to twelve hours for from twenty-four to forty-eight hours, followed by 0.25 Gm. every six hours for from forty-eight to seventy-two hours, and then increasing to a total of 0.5 Gm. every six hours, providing that no untoward reactions occurred. In these patients treatment was prolonged to from fourteen to twenty-one days, giving total dosage of from 18 to 25 Gm. Smaller daily dosage in several courses with rest periods between are being given to several patients whose improvement from one or more previous courses have been inadequate or only temporary. Alternation with sulfonamide compounds or combined treatment with other antibiotics may be necessary in some refractory cases. Whereas parenteral administration would obviate side-effects to a large degree, it does not lend itself well to treatment of ambulatory patients.

In the meantime efforts to improve the purity of the product have been at least partially successful. Some patients unable to tolerate earlier preparations were able to take subsequent product with little or no difficulty. Aureomycin base, instead of the hydrochloride, is currently under trial. A diluent containing L(−) leucine for intravenous administration of the hydrochloride also is under investigational use.

History of intrinsic or extrinsic allergy or intolerance to food or drugs, including sulfonamide compounds and other antibiotics, was of no apparent value in selecting patients for treatment with aureomycin. Side-effects were entirely unpredictable, except for the fact that male patients tolerated the drug infinitely better than did females. In only 4 male patients among 31 was there

marked gastro-enteritis induced by aureomycin, whereas such symptoms, usually followed by mucous-membrane manifestations, occurred in 48 of the 79 female patients treated. In only one of the males were there mucous membrane manifestations The role of sex hormones has to be at least questioned because of this seemingly significant disparity between the sexes.

Capricious appetite was noted by many patients. The majority of these particularly desired protein food (several expressed voracious desire for meat in any form) but some wanted sweets, pickles, or other contrasting taste-producing foods One patient wanted great quantities of nuts, suggesting possible vitamin B deprivation.

Urticaria of a few hours duration occurred in three patients.

Antihistamine drugs had slight if any effect on the possibly allergic symptoms described. Aluminum hydroxide was of value in lessening gastric irritation Kaolin, bismuth, and pectin compounds proved to be soothing to the intestinal tract and apparently lessened diarrhea.

The mechanism of some of the side reactions is not clear The high *p*H of aureomycin hydrochloride could account for gastric, intestinal, and bladder irritation but not for mouth, throat, anal, and vaginal symptoms Since aureomycin is known to be effective against many Gram-negative bacilli as well as many cocci, it is possible that synthesis or assimilation of B complex factors in the bowel is interfered with by destruction of a large part of the normal intestinal flora Some patients noted that the stool was odorless while taking aureomycin, others noted that the odor was particularly offensive, and still others noted no change in odor Mucous membrane manifestations appeared as early as three days after initiation of treatment in a few patients, they cleared up rapidly in one patient to whom vitamin B complex was given parenterally after the appearance of symptoms It is possible that the mucous membrane manifestations and the rarely occurring abnormal bleeding are due to multiple vitamin deficiencies rather than to B complex deficiency alone. Parenteral administration of

all of the vitamins concomitantly with oral antibiotic therapy may be essential to prevent these various manifestations.

Aggravation of symptoms existing at the time of treatment with aureomycin or symptoms which had previously been attributable to *Brucella* infection or allergy, were noted in the majority of patients. Backache, headache, muscle and joint pains and swelling, pain in various lymph nodes throughout the body, and increased fatigue, recurred in from moderate to severe degree, apparently through temporary increase in *Brucella* allergy. During the latter part of the course of treatment and following its discontinuance there was evidence of markedly decreased allergy. This was particularly noteworthy in two veterinarians and one cattle dealer, all of whom continued in contact with infected cattle, with freedom from symptoms for the first time in many years. In one of the veterinarians a markedly swollen, painful metacarpophalangeal joint returned to a normal, symptomless status during the three weeks course of aureomycin. This joint had been progressively involved for a period of two years prior to treatment as a complication of chronic brucellosis of at least ten years duration. It had previously been favorably influenced by desensitizing doses of *Brucella* B A.C. (Hoffmann) but only when the patient avoided contact with cattle It is not clear whether desensitization to *Brucella* is accomplished by bacteriostatic effect of aureomycin on *Brucella* organisms or by other mechanisms *Brucella* antigens usually provoked less allergic response following aureomycin

No apparently significant pattern of phagocytosis of *Brucella* following aureomycin therapy was noted.

No lasting ill-effects definitely attributable to aureomycin were noted Blood elements apparently were not affected There was no evidence of renal or central nervous system changes.

In an 8-year-old child, apparently moribund with a febrile illness of unknown etiology (possibly *Brucella* infection but probably endocarditis of other origin), aureomycin was given pending cultural studies The child survived Marked leucopenia and almost complete disappearance of polymorphonuclear forms (1,000

white blood cells with 1 per cent polymorphonuclears) was noted on the sixth day, at which time aureomycin was discontinued and penicillin substituted. Against aureomycin as the cause of the agranulocytosis was the fact that the total white blood count and neutrophile content had been steadily decreasing prior to administration. No reports of agranulocytosis have appeared in the literature to date

Perforation of a previously undiagnosed and unsuspected prepyloric ulcer occurred in a 28-year-old woman. The diagnosis was not confirmed surgically, the patient recovering under conservative treatment Known lesions of the stomach or duodenum may constitute contraindications to oral aureomycin.*

Results of treatment cannot yet be assessed with any degree of certainty, as of June 1, 1949. Relief of symptoms referable to chronic brucellosis has occurred during the course of treatment or soon thereafter in a majority of patients who were able to tolerate the drug. However, some patients have relapsed and some have had or will be given subsequent courses of aureomycin A small percentage have been uninfluenced by the drug; in some of these patients the diagnosis as to active chronic brucellosis was questionable

In summary it can be said that aureomycin orally will usually terminate the acute febrile illness, probably through bacteriostasis. By the same mechanism, with perhaps the additional factor of desensitization, partial to complete recovery from the chronic illness can be brought about in the majority of patients Because of the relapsing nature of brucellosis and because no criteria of cure are available, caution must be used in assessing results of this method of treatment. Repeated courses of treatment have been necessary in several patients, with apparently cumulative progress following each course. Optimum dosage remains to be determined

* Herrell and Barber (*Proc Staff Meetings, Mayo Clinic* 24 144, 1949) reported that 2 patients suffering from acute brucellosis and peptic ulcer tolerated aureomycin without difficulty

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brucellosis; the patients entertained great hopes for the outcome of treatment There were no dramatic results in this group. This is not conclusive since the type or severity of the neurosis may have been such as to preclude abandonment of symptoms under any circumstances, on an unconscious level. In others with neuroses of other types and lesser severity, *improvement could well* occur on such a basis, adding to the problem of evaluation of treatment effect. Fortunately, results of treatment in the majority of patients ultimately can be evaluated because of the existence of more or less characteristic physical and laboratory evidence of brucellosis and absence of evidence of psychologically determined illness

COMBINED USE OF ANTIBIOTICS

Heilman (*Proc. Staff Meet, Mayo Clinic.* 24:133, 1949) reported that aureomycin or chloromycetin was not particularly effective in reducing the numbers of *Brucella* in the spleens of infected mice Sulfonamide combined with aureomycin did not better the result. Aureomycin combined with streptomycin or dihydrostreptomycin was the most effective but did not eliminate all of the organisms.

Herrell and Barber (*Proc Staff Meet, Mayo Clinic* 24 133, 1949) gave dihydrostreptomycin parenterally, 1 0 Gm. twice daily, and aureomycin orally, averaging 3 0 Gm. daily, concomitantly over a period of twelve to fourteen days to 4 acutely ill males with recovery in all. In a personal communication of May 13, 1949, Herrell stated that all had remained well during periods of observation of from three to eight months following treatment. Six other patients also had been treated.

Of the 2 female patients with chronic brucellosis to whom this combined therapy was given by the author, one vomited and had to discontinue the aureomycin on the third day The other tolerated the method well

Dihydrostreptomycin and a sulfonamide compound may prove to be the most effective method of eradication of the organism

CHLOROMYCETIN *

Chloromycetin is a pure crystalline antibiotic obtained from cultures of *Streptomyces venezuela* and can also be prepared synthetically. Its reaction is neutral.

It has been used in 25 patients with culturally negative chronic brucellosis, some of whom had been unable to tolerate aureomycin Dosage was 2 to 4 Gm. daily with a total of 25 Gm. Clinical effects were similar to those of aureomycin, with only temporary response in several. The larger dosage may be more effective. There was relative freedom from side-effects except in a few patients in whom oral mucous membrane lesions or vaginitis developed, within 48 hours in one patient. In a few other patients a fleeting sunburn-like erythema, in areas previously or currently exposed to the sun, tachycardia, urinary frequency, metallic taste and heavily coated tongue, or slight initial diarrhea followed by constipation, were noted. There was a marked change in the intestinal flora. (See page 544.)

There was no improvement in the joint condition in 3 patients suffering from chronic brucellosis and rheumatoid arthritis, following aureomycin or chloromycetin. One developed a fleeting eosinophilia of 10 per cent following aureomycin and 22 per cent following chloromycetin

Skin necrosis 2 5 cm. in diameter, stationary for two months following skin testing, healed within a few days following chloromycetin therapy, suggesting a marked desensitizing effect

The possible psychologic effect of antibiotics, which have received so much premature publicity in newspaper and magazine articles, cannot be entirely discounted. However, aureomycin or chloromycetin was given to several patients in whom important degrees of psychoneurosis coexisted with evidence of chronic

* Acknowledgment is made to Parke Davis & Company for supplies of chloromycetin for use in chronic brucellosis and to Dr E A Sharp, Medical Director, for helpful suggestions as to its use

chiatrist is desirable, it should be said that a greater awareness of the possibility of human error is necessary. The accurate differentiation of chronic brucellosis from other somatic or from psychogenic illness may require an inordinately long time in some instances, in others it may be all but impossible.

The problem peculiar to the chronic illness is to determine not only whether the patient has been infected but whether recovery or cure has been achieved. In that respect it is not unlike tuberculosis or syphilis but experience with these diseases have been richer and expertness has been achieved by many more clinicians.

Medicine has not yet become so exact a science that a positive diagnosis can always be established, even after prolonged and expert study. Patients given a firm psychiatric diagnosis may succumb to an undiscovered somatic illness. Others, in whom there is little doubt of the physical nature of the illness, may develop unmistakable signs of psychiatric illness which only in retrospect can be recognized as having long existed in preclinical form In case of serious doubt there may be advantages in the delay incidental to a trial of treatment, somatic or psychiatric. If it is successful, the gain is obvious. If it fails, the patient may have gained insight and greater willingness to cooperate further.

Much effort may be expended in bringing a patient to see the psychogenic nature of an illness only to find that it is not treatable by any known psychiatric method. The ground has thus been literally taken from beneath the patient's feet and no substitute offered. In the borderline psychotic and in some psychoneuroses which are not amenable to treatment by present methods, the patient may secure a necessary degree of relief by the somatic expression of psychologic problems Much harm may be done in the attempt to persuade them to face intolerable situations The patient and his total illness must be treated—not one aspect alone.

The most careful judgment must be used to institute the regimen most likely to bring about early recovery in the individual under treatment Just how to do it in all cases is still not within the author's knowledge The clinician can be guided by the re-

Because of the continuing controversy as to the existence of prolonged chronic brucellosis, the value and significance of the individual laboratory procedures, and treatment methods, additional comments are necessary.

Broad generalizations concerning the diagnosis and treatment of chronic brucellosis cannot safely be made The patient must have the advantage of individual study. Hospital care theoretically affords the best opportunity for such study, including repeated cultural procedures, but the necessary degree of cooperation between the internist, psychiatrist, other specialists, and laboratory personnel rarely is achieved on a busy hospital service For many patients who are able to continue at their regular occupations it is not economically feasible. For others it is of questionable merit psychologically. Release from hospital with the statement that "the diagnosis of brucellosis has been ruled out" or that "the diagnosis is psychoneurosis" is a frequent and frustrating experience. In the one instance the patient is told only what the hospital staff thinks does not exist. In neither circumstance is the patient given constructive advice that is likely to lead to recovery.

It has recently been stated (*Technical Bulletin of the Veterans Administration* 10:49, February 28, 1949) that reliance should be placed upon the blood agglutination reaction and upon blood cultures, that if both are negative there is little to gain by eliciting a positive skin test (or by employment of the opsonocytophagic reaction) There is, however, reliable evidence that the employment of all available tests can result in a higher percentage of accurate diagnoses The collateral tests need not mislead the investigator but should, as expressed by Dr Howard A Rusk, serve as "straws in the wind," to supplement other information

The controversy may go on for as long as brucellosis continues to occur. The difficulties involved in making a correct diagnosis and in thus arriving at the proper treatment method have been stressed throughout this monograph In addition to the recommendation that a blending of the viewpoint of internist and psy-

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sults of purely objective scientific research and by scientific knowledge but cannot always apply them to the patient.

Vaginal, vulval, perineal and peri-anal changes, with intense itching and fissuring of mucous [illegible]

[illegible] or repeated courses administered. In the five patients in whom vaginal exudate was cultured, *Candida (Monilia) albicans* was recovered in all. Use of fungicidal agents resulted in disappearance of the lesions. In one patient who had been treated with inordinate amounts of aureomycin over a period of more than three months because of a suspected chronic brucellosis, the process had continued unabated for four months after therapy had been discontinued Early resolution followed use of a fungicide.

Overgrowth of apparently more virulent *Candida* may result from the destruction of normal intestinal organisms, thus favoring their growth in tissues deprived of resistance by lowered vitamin reserves. Cultures of oral and throat lesions to determine the possible role of *Candida (Monilia) albicans* in their persistence have not been concluded.

The lesions described are self-limited in most patients but the possibility of more or less permanent changes in intestinal flora is suggested

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